Routine follow-up after laryngeal cancer treatment

The assessment of pre-symptomatic recurrence detection

Savitri C. Ritoe

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The assessment of pre-symptomatic recurrence detection

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Voor mijn papa en mama

Part I

General introduction

Chapter 1

Routine follow-up after laryngeal cancer treatment, considerations and pitfalls

Follow-up after oncologic treatment or secondary screening

Routine follow-up after treatment of a primary malignancy that is meant to be curative is a form of screening.

The only way to detect primary malignancies and recurrences in an asymptomatic stage is to carry out a structured screening program. The hypothesis that asymptomatic detection leads to increased survival applies equally to patients with a recurrent tumor following prior treatment and patients with a primary tumor in population studies. Screening as it is carried out for primary tumors in the general population can be called *"primary screening"* while screening for recurrent cancer can be defined as *"secondary screening"*.

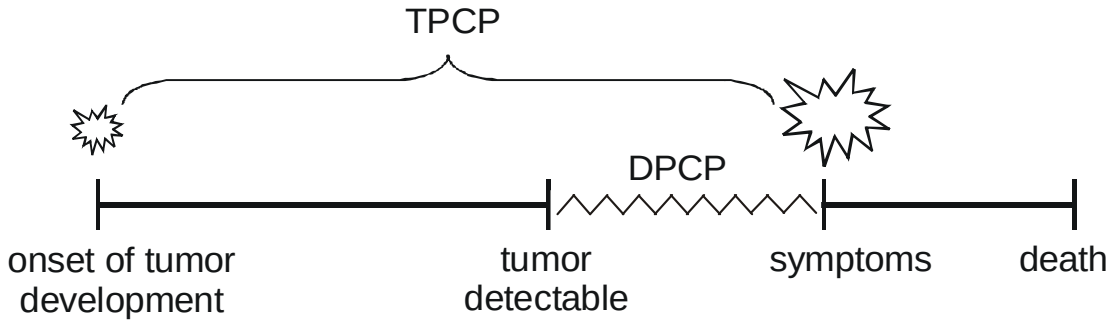

Figure 1. Diagram showing the natural course of cancer progression in relation to the implementation of a screening program.

The principles on which both primary and secondary screening are based are shown graphically in Figure 1. At the beginning of tumor development, the tumor is too small to be detected by means of the diagnostic techniques used. In the course of time and as the tumor volume increases, the tumor becomes detectable but has not yet generated any tumor-specific symptoms. The phase from the start of tumor development to the appearance of symptoms is called the "Total Preclinical Phase" (TPCP); the beginning of this phase is at a moment in the life of the future patient that cannot be established more accurately, while it ends at the moment that the patient seeks help because of the appearance of symptoms caused by the tumor.[1,2] Starting at some specific point, the tumor becomes detectable and the phase from this point to the appearance of symptoms is called the "Detectable Preclinical Phase" (DPCP). This phase ends at the same moment as the TPCP. The beginning is determined in essence by the sensitivity of the test employed. It is obvious from the above that screening is senseless if the DPCP is

very short and patients develop symptoms relatively quickly after the development of a primary malignancy or recurrence. One can imagine that in such a case, there will be little difference in therapeutic options and survival between asymptomatic and symptomatic patients.[1] Ultimately, symptoms appear and the clinical phase starts. According to the hypothesis, the chances of survival are lower in the clinical than in the preclinical phase.
The most important difference between primary and secondary screening is that the percentage of recurrences following oncologic therapy is often high in comparison with the percentage of tumors detected by screening in the general population. This high percentage of recurrences has often been cited in the past as a reason for implementing a follow-up program after treatment of a primary malignancy.

Since the start of the first population studies for the early (asymptomatic) detection of cancer, there has been debate regarding the efficacy with respect to the achieved gain in health.[3-8] Up to the present, doubts are sometimes expressed regarding the ultimate reduction in cancer mortality and the increased survival as a result of population studies.[9-11] The injurious effects of overdiagnosis and overtreatment due to screening programs are often emphasized. Screening is generally an expensive proposition and can result in emotional stress for the target group.[4]
That early detection can lead to a better prognosis and lower morbidity has been proven or at least shown to be highly probable for a number of diseases.[4,12] One of the emotional arguments in favor of screening programs is that every life saved makes the screening of the entire population worthwhile. Doctors sometimes maintain that questioning the utility of post-oncologic screening is the same as suggesting that patients who have had a life-threatening disease should receive poorer management. They unfortunately often do not realize that there is usually very little time for psychosocial guidance during the present follow-up programmes.[13]
According to Cole and Morrison (1980), successful screening demands not only an affordable sensitive test and a screening program that can be implemented easily, but also a fitting disease for which the population is screened. This disease must have serious consequences for the future patient, the treatment given must be more effective if it is given in the asymptomatic stage, and the prevalence of persons in the DPCP must be high.[1]

One of the most important problems in the implementation of both primary and secondary screening programs is that tumors are also detected that grow slowly and would never have become a malignancy that requires treatment.[10,14] This can result in a situation in which the patient is exposed to treatments for tumors that would possibly have had little or no effect on life expectancy.[10] Such treatments can lead to an increase in both morbidity and mortality. In addition, it has occasionally been suggested that screening may lead to the use of more aggressive forms of treatment. As a result of screening for breast cancer, for example, the number of patients with a mastectomy is said to be increasing.[10] The effects of the morbidity and mortality as a result of screening are difficult to assess and are usually omitted from consideration during the evaluation of screening programs.

Another pitfall that must be considered during the evaluation of primary and secondary screening programs is the type of tumor detected by follow-up examinations. It has been suggested that the aggressive tumors that grow rapidly and metastasize may also generate symptoms rather rapidly, so that the screening interval is short. The chance that such a malignancy will be detected in a symptomatic stage outside of the routine follow-up may therefore be high. The less aggressive tumors may generate symptoms less quickly, so that the screening interval is longer. These tumors are therefore detected during routine follow-up in an asymptomatic stage. However, in view of the low degree of malignancy, the moment at which treatment is started, in the symptomatic or the asymptomatic stage, may also be less important.

On the other hand, it may also be the case that the presence or absence of symptoms actually says little about the degree of malignancy but is determined mainly by the location of the tumor. A tumor that has not yet generated any symptoms may nevertheless already have produced distant metastases, which are usually incurable.[15]

A program for oncologic follow-up is often implemented for years on end without ever having been proven to be effective in the detection of tumors in an asymptomatic stage. When doctors notice that screening programs, especially secondary ones, are having little effect, they may be tempted to resort to the use of more refined diagnostic technology during screening, such as routine MRI-scans and PET-scans. In addition to the fact that this can lead to an exponential increase in the costs, the number of false-positive results usually also rises.

Finally, during the implementation of secondary screening programmes, no consideration is generally given to the question whether there is indeed a curative treatment available for a recurrent tumor, whether detected in the asymptomatic stage or not. On the basis of the considerations presented above, it can be concluded that a uniform follow-up program must be adjusted to the individual patient, taking a variety of factors into consideration. An attempt could be made to provide “custom-tailored care”, as was recently recommended by the Queen Wilhelmina Fund.[16]

Follow-up after the treatment of laryngeal cancer

In 2005, a primary laryngeal carcinoma was detected in 702 patients in the Netherlands: 572 men and 130 women. For the time being it is estimated that, particularly as a result of the aging of the population and the predicted increase in the incidence of laryngeal cancer in women, the prevalence of laryngeal cancer will continue to increase until 2015.[16] This has implications for the relationship between supply and demand in healthcare and it would seem an appropriate time to assess the value of the current intensive follow-up program.

The publication “Richtlijn Larynxcarcinoom” [Laryngeal carcinoma guideline], based on the results of the guideline meeting of the “Nederlandse Werkgroep Hoofd-Halstumoren” (Netherlands Working Group Head & Neck Tumors; NWHHT) and the “Kwaliteitsinstituut voor de gezondheidszorg” (Institute for Healthcare Quality; CBO), was published in 2000.[17] In this guideline, the main goal of the implementation of a fixed follow-up program is stated to be: the early detection (before the patient develops any symptoms) of a local or regional recurrence. The secondary goals are said to be: the early detection of primary tumors in the head & neck region, the esophagus or the lower respiratory tract and the early detection of metastases. Other goals mentioned include the psychosocial guidance and rehabilitation of the patient, the evaluation of one’s own actions, and the registration and treatment of complications. Just as in the case of so many other follow-up programs, the follow-up program after treatment of laryngeal carcinoma has been carried out on a national scale for decades without any evident scientific proof of its efficacy in relation to the stated goals.
There is thus a national consensus regarding the frequency of the routine follow-up examinations (22) and the duration of follow-up, at least 5 and at most 10 years (Table 1). In the UMCN St. Radboud, this follow-up program has already been

implemented for decades.[18,19] Until the introduction of the "Laryngeal carcinoma guideline 2000", X-rays of the lungs were routinely made in order to detect primary lung carcinoma with an interval of 6 months during the first 2 years of follow-up, followed by an annual chest X-ray up to 5 years after the end of treatment.

Table 1. Follow-up schedule

	Follow-up year					
	1st	*2nd*	*3rd*	*4th*	*5th*	*6th-10th*
Interval between routine visits (months)	2	3	4	6	6	12
Frequency of routine visits/year	6	4	3	2	2	1
Interval between chest X-rays (months)	6	6	12	12	12	0
Chest X-ray frequency/year	2	2	1	1	1	0

In dark grey: these numbers are taken from the follow-up schedule recommended by the current guidelines.[17]

As part of the evaluation of the follow-up program for patients with laryngeal carcinoma, as described in this thesis, we first looked critically at the degree to which the routine follow-up that is offered is also taken advantage of by the patient. For that purpose, all of the routine follow-up visits were counted and compared with the expected number of routine follow-up examinations in a cohort of 402 patients in the period from 1990 to 1995. It turned out that 98% of the expected routine follow-up examinations had actually taken place.[19] The evaluation of the follow-up program becomes more difficult later in the follow-up period because each patient develops his or her own rhythm with regard to the moments of follow-up (Figure 2).

Aims of this thesis

According to the "Laryngeal carcinoma guideline 2000" of the NWHHT and the CBO, the main goal of the present follow-up program is the detection of local and regional recurrences in the asymptomatic stage. To date, there is no proof for the effectiveness of routine follow-up with regard to an improvement in life expectancy and a reduction in cancer-specific mortality among patients that develop a local or regional recurrence.

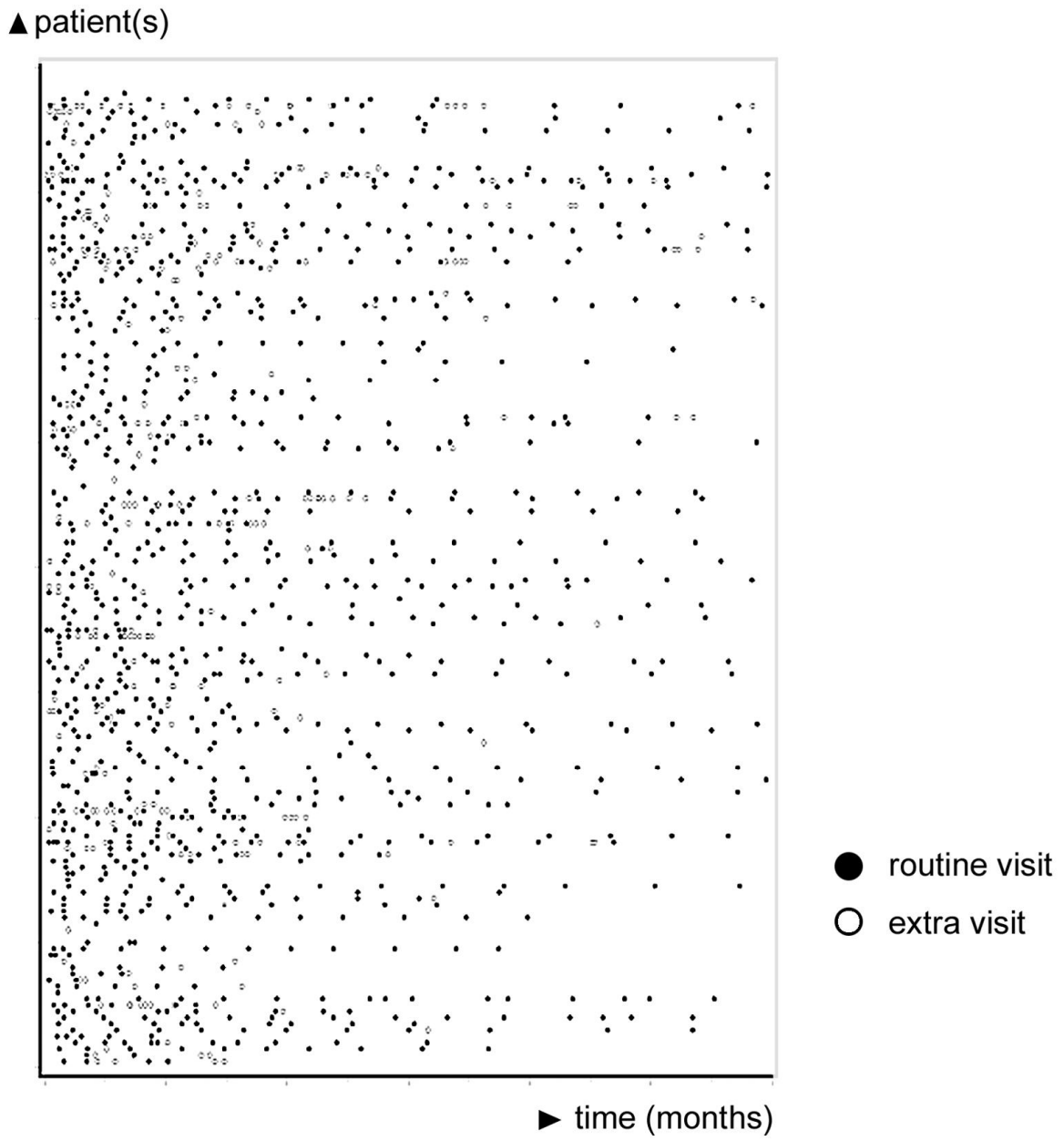

Figure 2. The number of follow-up examinations per patient (n=156) up to the detection of the recurrence during the first 3 years of the follow-up programme.

The aim of this thesis is to investigate the effectiveness of routine follow-up for patients with laryngeal cancer, keeping in mind that the routine follow-up program is also implemented for a number of secondary goals such as the detection and treatment of complications and the provision of rehabilitation and psychological support. However, the effectiveness of the follow-up program with regard to these secondary goals has not been investigated in this thesis.

This thesis will attempt to answer the following questions:

- to what extent are the follow-up examinations that are routinely agreed upon actually carried out and acted upon?
- what is the percentage of asymptomatic recurrences detected in the present follow-up program?
- is there a difference in the purpose of treatment, the therapy offered, the survival time and mortality between patients in whom a recurrence is detected in the symptomatic stage and those in whom a recurrence is detected while still asymptomatic?
- is the screening for primary lung tumors appropriate?
- is it suitable to offer the same strict follow-up program to patients for whom there are few therapeutic options left in case the tumor recurs?
- can we make a distinction, in the current population of patients with larynx cancer, between a low-risk and a high-risk group regarding the development of a local and/or regional recurrence? What is the lead-time in the present follow-up program and what can be expected with regard to the detection of asymptomatic recurrences if the number of routine follow-up examinations is varied?
- is it possible, with the aid of a decision theory model, to predict the impact on life expectancy and cancer-specific mortality if the routine follow-up were to be eliminated completely?

Outline of this thesis

Chapter 2 deals first of all with the question whether the follow-up program is actually implemented in daily practice. A cohort study was carried out in which patients with either an asymptomatic recurrence or a primary tumor, detected by a routine follow-up examination, were compared with patients that had already developed symptoms. Insight is provided into how many recurrences are actually detected by follow-up examinations before they develop symptoms. The therapy offered, the purpose of treatment, the survival and the cancer-specific mortality are evaluated and compared in asymptomatic and symptomatic patients.
Chapter 3 is devoted to the suitability of the early detection of a primary lung carcinoma in patients that have already been treated for laryngeal cancer. Here again, patients whose tumors were detected on a routine chest X-ray while in the asymptomatic stage are compared with patients whose tumors were detected

while already symptomatic with regard to the therapy offered, the survival and the cancer-specific mortality.

The general follow-up program is offered both to patients that have already received extensive treatment for laryngeal cancer and to patients with less extensive tumors. *Chapter 4* describes a cohort of patients that have undergone total extirpation of the larynx with or without additional radiotherapy. Those who developed recurrent cancer were studied with regard to the remaining therapeutic options, how many could be treated curatively and what the life expectancy was. The suitability of routine follow-up for this specific group of patients was examined.

In *Chapter 5* we attempt to make a distinction between a high-risk and a low-risk group with regard to the development of a local and/or regional recurrence, based on clinical factors. The lead-time in the current follow-up program with the present diagnostic techniques is estimated. What percentage of asymptomatic recurrences can be expected to be detected if the follow-up program were intensified?

Finally, in *Chapter 6,* with the aid of a previously validated Markov model, a cohort simulation is carried out for four hypothetical patient groups that differ in age.[20] The life expectancy and cancer-specific mortality are calculated, using the data for percentage recurrence and mortality in current practice. Subsequently, the effects of the elimination of routine follow-up on the life expectancy and cancer-specific mortality are calculated.

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Part II

Asymptomatic cancer detection

Chapter 2

Value of routine follow-up for patients cured of laryngeal carcinoma

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Cancer 2004;101:1382-1389

Abstract

Background.
Routine follow-up offered to patients with laryngeal carcinoma in the Netherlands consisted of 22 routine visits over a time period of 10 years after treatment. The primary aims of the follow-up program were to detect cancer recurrence in asymptomatic patients and to achieve better survival outcome by reducing cancer-specific mortality rates.

Methods.
A longitudinal cohort study was performed to evaluate the effect of this follow-up schedule. Between January 1990 and January 1995, the authors studied all patients with primary laryngeal squamous cell carcinoma who were treated with intention to cure. For patients who developed cancer recurrence, all routine and extra visits were documented. Reported symptoms and physical evidence of tumor were mapped.

Results.
The patients complied with the follow-up protocol closely. In only 2% of all routine visits an asymptomatic cancer recurrence was found. There was no difference in survival and tumor mortality rates for patients with and without symptoms, despite the difference in whether the therapy applied had the intention to cure. It seemed that patients who developed tumor recurrence after therapy for laryngeal carcinoma received no benefit from screening for cancer recurrence. The lack of benefit for cancer screening, among asymptomatic patients, might be explained by unfavorable tumor biology parameters.

Conclusions.
The routine follow-up program after treatment for laryngeal carcinoma did not lead to survival benefit for asymptomatic patients with tumor recurrence.

Introduction

The aim of offering multiple routine follow-up appointments after curative treatment for cancer has been the subject of many publications.[1–6] The duration of follow-up, the intensity of the routine visits, and the diagnostic tools applied are frequently based on common acceptance rather than empiric evidence.[6] Supporters of follow-up programs base their view on the assumption that asymptomatic patients with cancer recurrence will have better therapeutic options, improved survival rates, and decreased cancer-specific mortality rates.

The follow-up program also can be used to collect data on complications and to gain insight into the results of the treatment applied. Another important reason for the follow-up program is the mental guidance of the patient and the contribution of this period to the relationship between physician and patient.

The underlying reasons for offering routine follow-up to patients with cancer after treatment are to a certain extent comparable with those for performing cancer screening programs in the general population. Various issues should be considered when applying a follow-up program for early cancer detection.

The aim of screening is to reduce mortality and/or morbidity through early detection of cancer when patients are asymptomatic. Many studies on this topic refer solely to the gain in time from the first diagnosis of cancer recurrence to death to prove the benefit of the screening program. However, this measurement involves a pitfall, namely, that the date of the detection of the tumor merely has occurred earlier, but the date of death has not been postponed. This phenomenon is called lead time bias.[7]

A second pitfall is caused by tumor biology. Screening programs are based on the assumption that asymptomatic patients with tumors will have a lower stage of disease compared with symptomatic patients. This assumption has been proven for some patients with primary malignancies, but it is unknown whether this also applies to patients with cancer recurrence. Small tumors may have already spread beyond the primary site. Screening programs would, therefore, only detect naturally slow-growing tumors that have fewer tendencies to spread. This phenomenon is called the length bias.[8]

Screening also has several disadvantages. First, patients may be confronted with non curable malignancies (often distant metastases) and tumors that otherwise would have remained silent and not influenced the cause of death. Second, false-positive screening results may increase medical costs. Third, some patients might adhere so closely to the follow-up schedule that detection of tumor recurrence is delayed because they waited until their prescheduled visit to the physician.

Similarly, some patients who develop symptoms shortly after a prescheduled visit may even ignore them because they have recently been reassured. Symptomatic patients with cancer who have not been screened should be analyzed separately.[9]

Materials and methods

Study

In The Netherlands (a total population of 16 million people), the incidence of laryngeal carcinoma amounts to 700 new patients each year. Most patients (68%) can be cured.[10,11] All patients treated for laryngeal carcinoma in The Netherlands are offered routine follow-up. In the year 2000, a nationwide guideline was introduced that contains recommendations for diagnostic tools, treatment, rehabilitation, and follow-up for patients with laryngeal carcinoma.[12] The follow-up schedule in this guideline is the same as the protocol that has been used by the Head and Neck Oncology Group at the University Medical Center Nijmegen for > 25 years. According to this schedule, recently treated patients with laryngeal carcinoma visit our clinic regularly, i.e., 22 times over a period of 10 years. In the first year of follow-up, the patient has a routine visit every 2 months (6 times a year). In the second and third years, the patient is seen every 3 months (4 times a year) and every 4 months (3 times a year), respectively. In the fourth and fifth years, the patient is seen twice a year and thereafter up to 10 years, the patient is seen once a year. As patients with laryngeal carcinoma run a high risk of developing lung carcinoma, seven routine chest X-rays are taken regularly for the early detection of lung malignancies.[13] During the follow-up period, patients are free to visit the clinic in between prescheduled visits if they develop symptoms.

The current study was performed to evaluate the follow-up program. A comparison was made between the patients with screen-detected tumor recurrence or second primary tumors in the larynx, lung, or different body site and those with a tumor detected due to reported symptoms. Data were gathered to evaluate whether the follow-up (screening) program brought forward the detection date of the tumor, whether asymptomatic patients with a malignancy were offered better therapeutic options, and whether this improved the survival outcome.

Methods

A longitudinal study was performed. All consecutive patients who were referred to our clinic between 1990 and 1995 with laryngeal carcinoma were included in the

study if they met the following inclusion criteria: primary tumor of the larynx, histologically proven squamous cell carcinoma, initial treatment had curative intent.

At each prescheduled follow-up visit, an interview was performed and patients received a complete physical examination of the head and neck. This included palpation of the neck region, laryngoscopy, and pharyngoscopy.

Patients' medical records from both the Department of Otorhinolaryngology and the Radiotherapy Department were examined. All routine and extra visits by patients who developed local or regional tumor recurrence, a second primary cancer, or distant metastases were documented and recorded in a relational database (Microsoft Access). At each visit, the precise symptoms that indicated tumor and/or physical evidence of tumor recurrence were scored. The diagnostic tools used and test results were also recorded. For each tumor detected during follow-up, it was specified whether that tumor had led to specific symptoms and whether it had been detected during a prescheduled routine visit or during an extra visit initiated by the patient. To evaluate the follow-up program, we used the data on the first tumor recurrence or second tumor in the head and neck region or elsewhere in the body. Data recorded after this point in the routine follow-up schedule were disregarded.

The follow-up program is intended to detect cancer recurrence at an early stage in asymptomatic patients. In the evaluation of the benefit of such a program, patients who already have symptoms indicating cancer should be analyzed separately. Therefore, for all patients with tumor recurrence, it was noted whether there had been any symptoms specifically indicating the malignancy at the time of detection. By classifying each tumor (cancer recurrence or second primary malignancy) according to the type of visit (routine or extra) in which it was detected and according to the presence of specific symptoms, patients were divided into three groups. In Group I, tumors were detected at a routine visit and patients had no reported symptoms. In Group II, tumors were detected at a routine visit and patients reported specific symptoms. In Group III, tumors were detected at an extra visit and patients reported specific symptoms.

Patients whose tumor recurrence was detected during admission to the hospital for other reasons, such as cardiac problems, or patients in whom it was not clear whether they had existing symptoms or not, were excluded from our analysis. The three groups were compared on therapeutic options available, cause of death, and survival.

Survival analysis was performed using the Kaplan–Meier method. The log-rank test was used to calculate differences between survival curves. For categoric and

ordinal data, we compared the three groups with the use of the Fisher exact test. All statistically tests were two sided. $P \leq 0.05$ indicated statistically significance. Analyses were performed with SPSS software, Version 11.0 (SPSS, Chicago. IL).

Results

Population Parameters

A total of 402 patients with laryngeal carcinoma were studied. Most patients had glottic laryngeal carcinoma (62.7%), 37.1% had supraglottic laryngeal carcinoma, and only 1 patient (0.2%) had subglottic laryngeal carcinoma. The peak incidence was in the seventh decade of life and the man-to-woman ratio was 8.6: 1.0. For 373 patients, the laryngeal tumor was a primary malignancy. Three of the remaining patients had been cured of lung carcinoma, another 3 patients had been successfully treated for malignancies in the head and neck region other than the larynx, and 23 patients had been cured of other malignancies. The mean follow-up was 61 months, with a median of 66 months. The 5-year overall survival rate of the 402 patients was 73%. Figure 1 shows the survival curves for the patients who developed tumor recurrence or a new malignancy and for the patients who remained malignancy free during the follow-up.

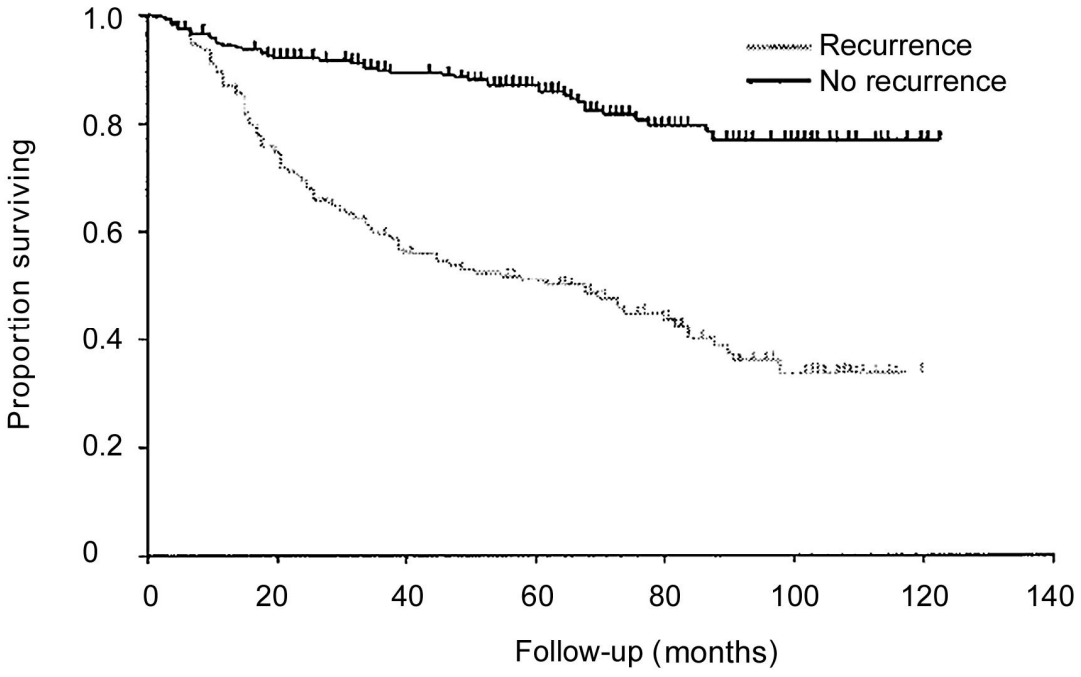

Figure 1. Survival curves for patients who developed tumor recurrence or a new malignancy and for patients who remained malignancy free during the follow-up.

The 5-year overall survival rate of the patients without a new tumor was 87% compared with 51% for the patients who developed tumor recurrence or another malignancy during follow-up, calculated from the detection date of the primary laryngeal tumor.

Follow-Up Protocol

The calculated expected number of routine visits in the study population of 402 patients was 4721. This number was corrected for the actual follow-up time of each patient by taking into consideration the date of death or detection of cancer recurrence. According to the medical records, the 402 patients made 4639 routine visits to our clinic. The number of actual visits shows that a realistic evaluation of the follow-up schedule is possible, because 98% of the planned routine visits took place.

Cancer Recurrence

Recurrence of laryngeal carcinoma or development of a second primary tumor occurred in 156 (39%) of the 402 patients. The greatest proportion of the malignancies found during the follow-up consisted of locoregional tumor recurrence. For 70 of 156 patients (44.9%), tumor recurrence developed at the primary tumor site, whereas tumor recurrence developed in the neck in 24 of the 156 patients (15.4%). Seventeen patients (10.9%) had a second primary cancer in the lungs and 15 patients (9.6%) had a second primary cancer in the head and neck region. Distant metastases were detected in 15 patients. Finally, in 15 patients, second primary malignancies developed elsewhere in the body.

In the 10-year follow-up program, 78% of the locoregional tumor recurrences, second primary carcinomas, and metastases developed in the first 3 years. The mean interval was 25.4 months. The median interval, however, was 15 months, which suggests that 50% of these tumors were detected in the first 15 months of follow-up. Only 20 (13%) malignancies were detected in the 6th to 10th year of the follow-up program (Figure 2).

Of the 156 patients with tumor recurrence, 138 were classified into 1 of the 3 groups described in Materials and Methods. Table 1 shows the number of patients in each group. To check whether the groups were comparable for further analysis, patient and tumor characteristics were compared: age, gender, primary tumor localization, tumor stage, histology, and therapy modality for the initial laryngeal tumor. There were no statistical differences in these variables among the three groups, except for gender. For example, for women, more tumor recurrences were detected during routine visits while symptoms were present. For men, however,

more tumor recurrences were detected during extra visits with symptoms present. However, the total number of women was too small to make a reliable comparison.

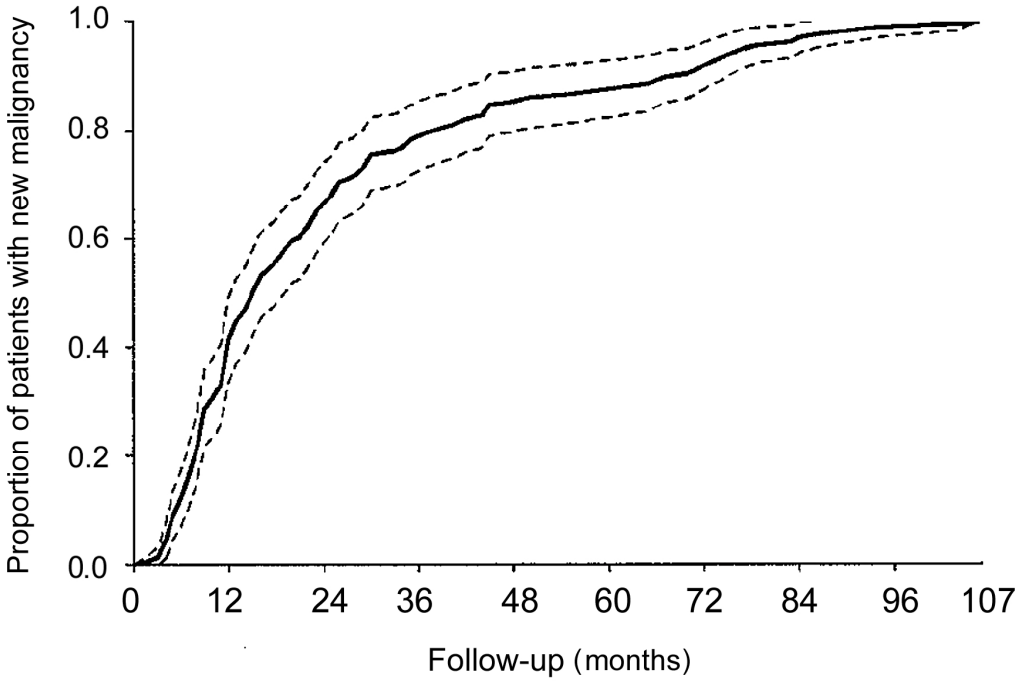

Figure 2. Time of cancer recurrence or second primary tumor detected during follow-up for 156 patients. Dotted lines represent the boundaries of the 95% confidence interval.

Table 1. Grouping of patients according to type of visit and presence of symptoms

Symptoms	Routine visit	Extra visit
No	37 (Group I)	4[a]
Yes	46 (Group II)	55 (Group III)
Unknown	11[a]	3[a]

[a] Patients were excluded when groups were compared.

There was no difference for age among the groups. The mean ages for Groups I–III were 64.9 years, 61.4 years, and 62.8 years, respectively. Table 2 presents the primary tumor characteristics for the three groups.

Table 3 shows the distribution of type of cancer recurrence in the three groups. There is a statistically difference for type of tumor recurrence (P = 0.001). Most locoregional cancer recurrences were found during routine visits while symptoms were present. The second primary lung tumors were mostly screen detected and metastases were predominantly found on extra visits while symptoms were present.

Table 2. Comparison of patient groups according to primary tumor characteristics.

	No. of patients[a]			
Characteristics	Group I (n=37)	Group II (n=46)	Group III (n=55)	P value for comparison between groups
Primary tumor localization				
Supraglottic	18 (29)	21 (33)	24 (38)	0.86
Glottic	19 (25)	25 (33)	31 (42)	
Tumor stage[b]				
I	9 (29)	12 (39)	10 (32)	0.11
II	10 (20)	22 (45)	17 (35)	
III	6 (22)	6 (22)	15 (56)	
IV	11 (38)	5 (17)	13 (45)	
T status[b]				
cT1	9 (29)	12 (39)	10 (32)	0.06
cT2	12 (21)	25 (45)	19 (34)	
cT3	6 (24)	4 (16)	15 (60)	
cT4	9 (37)	4 (17)	11 (46)	
N status				
cN0	28 (26)	40 (37)	41 (37)	0.36
cN1	5 (25)	4 (20)	11 (55	
cN2	4 (50)	2 (25	2 (25)	
cN3	0	0	1 (100)	
Histologic grade[c]				
I	3 (14)	12 (57)	6 (29)	0.19
II	22 (30)	17 (23)	34 (47)	
III	8 (26)	12 (39)	11 (35)	
Therapy[d]				
Surgery	4 (27)	6 (40)	5 (33)	0.05
Radiotherapy	28 (27)	39 (37)	38 (36)	
Surgery+radiotherapy	5 (20)	1 (5)	12 (67)	

[a] Numbers in parantheses show the percentage of patients divided between group I-III.
[b] Two patients excluded. T stage described as “invasive carcinoma”.
[c] I: well differentiated II: moderately differentiated; III: poorly differentiated.
Data unavailable for 13 patients.
[d] Therapy for the initial laryngeal tumor

Table 3. Distribution of recurrence type according to mode of detection.

Type of cancer recurrence	Group I	Group II	Group III	Total
Locoregional recurrence (%[a])	19 (22)	41 (48)	25 (30)	85 (100)
Percentage within group	53	89	55	
Second primary head and neck carcinoma (%[a])	3 (25)	1 (8)	8 (67)	12 (100)
Percentage within group	8	3	17	
Second primary lung carcinoma (%[a])	9 (53)	2(12	6 (35)	17 (100)
Percentage within group	25	4	13	
Metastasis (%[a])	5 (36)	2 (14)	7 (50)	14 (100)
Percentage within group	14	4	15	
Total no recurrences	37	46	55	128[b]

[a] Percentage of all documented recurrences of the specified type.
[b] Patients with other primary tumors were excluded.

Therapeutic Options

The three groups were compared to determine whether there were differences between therapies for recurrent or second primary tumors. For each patient, it was determined whether the therapy had a curative or palliative intent. In the current study, 70% of the patients in Group I (without symptoms, detected during a routine visit) received therapy with the intention to cure, 80% of the patients in Group II (with symptoms, detected at a routine visit) received therapy with curative intent, and 51% of the patients in Group III (with symptoms, detected during an extra visit) received therapy with the intention to cure. There was a statistically significant difference among the 3 groups (P = 0.007) regarding the therapy intention (curative or palliative) for the tumor recurrence or second primary tumor. However, there were no differences in the types of therapy modality applied and the percentage of patients treated with surgery, radiotherapy, or a combination of these two was comparable among the 3 groups (P > 0.05). Four patients were excluded from this analysis, because it was impossible to determine whether the therapy had been of curative intent.

For each type of cancer recurrence, except the second primary cancers (not located in the head/neck region or lungs), it was determined whether there was a difference in intention of therapy applied (curative or palliative) among the groups.

For locoregional cancer recurrence, no difference was found for intention to cure (P = 0.194). The second primary head and neck malignancies also showed no difference among the 3 groups for intention to cure (P = 0.182). The second primary lung carcinomas showed no difference in the aim of treatment among the three groups. However, there was a slight tendency that more patients in Group I were offered therapy with intention to cure (P = 0.09). Finally, only 1 of the 15 patients with distant metastases received therapy with the intention to cure.

None of the tumors showed a difference between the types of therapy applied (surgery, chemotherapy, or radiotherapy) and the mode of detection. This analysis was not performed for the patients with metastases because only 2 of the 15 patients received any form of therapy.

Cause of Death

Cancer-specific mortality was calculated and compared for the three groups. Cause of death was scored for all patients. Of the 20 patients in Group I, 18 (90%) died of cancer. In Groups II and III, 88% and 93% of the patients, respectively, died of cancer. There was no significant difference among these rates. Five patients were excluded because the cause of death was unknown (P = 0.89).

There were no statistically significant differences among the three groups for cause of death analyzed for each type of cancer recurrence separately.

Survival

Survival curves were calculated for the three patient groups and compared. First, survival was calculated, starting from the date of new tumor detection during follow-up. Of the patients in Groups I, II, and III, the 5-year survival rates were 32%, 45%, and 38%, respectively (Figure 3). The survival curves did not differ significantly ($P = 0.29$).

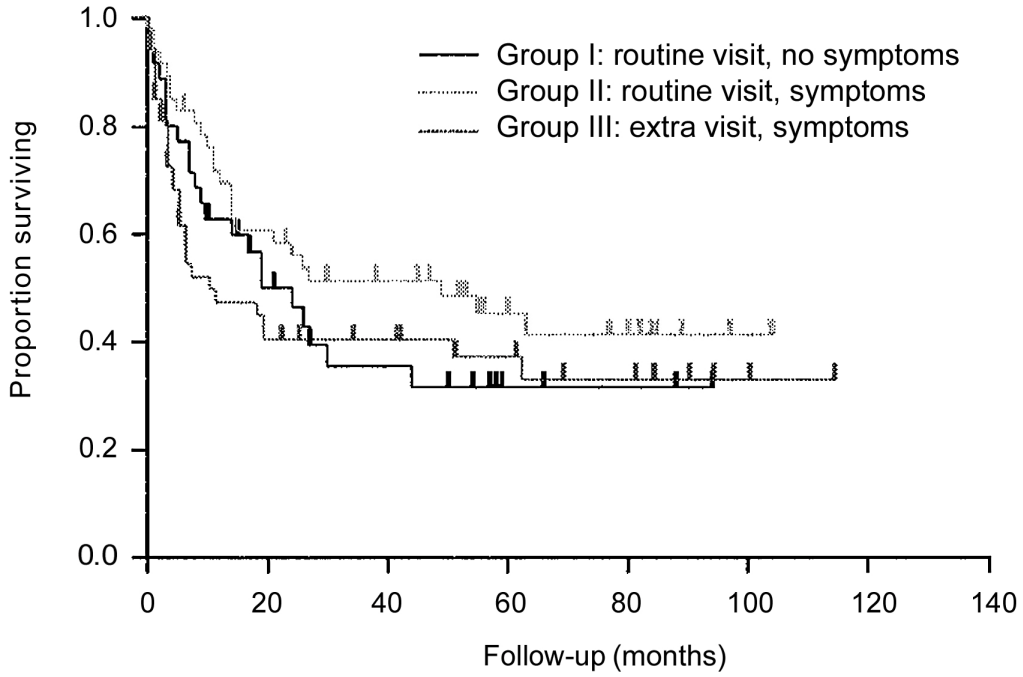

Figure 3. Survival plotted from the detection date of cancer recurrence or second primary malignancy.

Second, survival curves were calculated using the detection date of the primary laryngeal carcinoma as the starting point. The 5-year survival rates were 43%, 54%, and 53%, respectively, for Groups I, II, and III. There were no statistically significant differences ($P = 0.65$) among the survival rates of the 3 groups (Figure 4).

Patients with locoregional cancer recurrence, second primary head and neck carcinoma, second primary lung carcinoma, or metastases were compared for survival calculated from the primary laryngeal carcinoma by mode of detection. None of the malignancies showed a statistically significant difference.

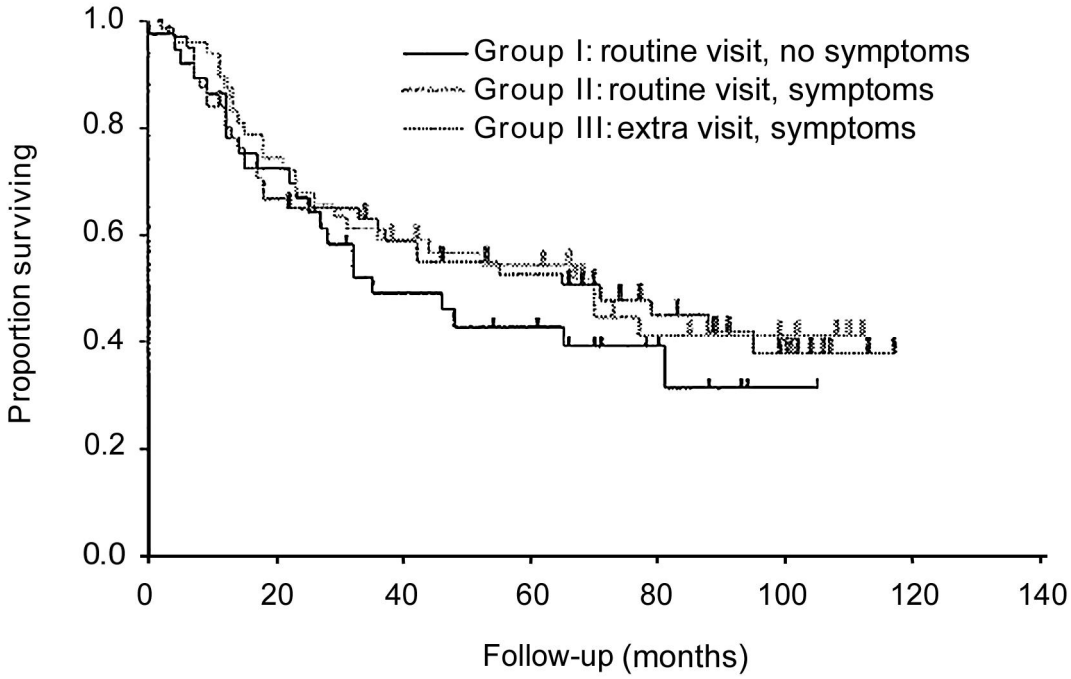

Figure 4. Survival plotted from the presentation date of the primary laryngeal tumor.

Discussion

The main reason for employing a follow-up program for patients who received treatment for cancer is to detect tumor recurrence in asymptomatic patients during the early stage. It is assumed that asymptomatic patients with cancer recurrence can be treated more successfully than symptomatic patients and that early treatment results in longer survival and less morbidity. Follow-up programs also are performed to reassure and guide the patient, to control and manage morbidity, and to identify and treat symptoms caused by distant metastases.

The current study shows that most cancer recurrences were detected in the first 3 years of the follow-up program. There is a statistically significant difference among the three groups for the intention of the therapy applied to treat the cancer recurrence. Patients in Group III were less frequently offered therapy with curative intent. This can be explained by the finding that most metastases are found in this group. The second primary lung malignancies were mostly screened by routine X-rays of the chest. However, a previous study showed no survival benefit for patients with asymptomatic lung cancer compared with patients with symptoms.[13] Neither the cause of death nor survival differed among the groups. No differences were found for cause of death or survival for the different types of malignancies.

Although the detection of primary cancer in asymptomatic patients at an early stage may have a positive effect on survival, detection of the tumor in asymptomatic patients after treatment for a primary tumor does not lead to a reduction in cancer-specific mortality rates. How can this be explained? It could be that the assumption that tumors in asymptomatic patients are detected at an early stage is false. A small tumor with aggressive features may cause few symptoms locally but may have already metastasized. Patients who develop a cancer recurrence may have a more aggressive type of cancer or are genetically more at risk of developing cancer. There has been a so called negative selection based on biologic tumor characteristics.

The number and frequency of visits in the follow-up schedule for patients with head and neck carcinoma are based on tradition, geographic location, and socioeconomic environment. Most studies that advocate follow-up for patients with laryngeal carcinoma merely focused on the high incidence of local cancer recurrence and second primary malignancies.[14–16] A few studies investigated whether the frequency of visits is wisely chosen and whether presymptomatic recurrence detection is advisable. These studies included patients with laryngeal carcinoma and other head and neck malignancies.[17–20]

The 402 patients in the study population visited the clinic for routine follow-up 4639 times. Thus, each patient returned an average of 11.5 times. For 94 of the 156 patients with tumor recurrence, the malignancy was detected during a routine follow-up visit. This means that for tumor detection, only 2% of all visits was effective. Patients with reported symptoms requested extra visits 1148 times. Ultimately, our clinic was visited 5787 times during the study period.

It can be questioned whether a detection rate of 2% is enough to maintain a follow-up program. Some will find this rate too low compared with the cost of the follow-up program, whereas others will say that the disease being screened is so serious and harmful that the low detection rate does not influence the decision to screen. For example, the rate of breast carcinoma detection by the nationwide screening program for women 50–69 years old is 1% at the first screening and 0.5% at consecutive screenings.[21] Other factors add to the complexity of this discussion. In our study, 78% of the patients with tumor recurrence (locoregional recurrence, second primary malignancies, or metastases) were detected in the first 3 years of the follow-up program. This casts doubt on the effect of the follow-up program from the 4th to the 10th year.

Patients with symptoms whose recurrence was detected during an extra visit were less likely to receive curative treatment. Nevertheless, the survival or cause of death in symptomatic patients with cancer detection did not differ from asympto-

matic patients with cancer detection. This is not consistent with the 1994 study of de Visscher et al.[17] In their follow-up study for squamous cell carcinoma of the larynx, pharynx, and oral cavity, asymptomatic patients with tumor detection had a better survival outcome than symptomatic patients with tumor detection. However, survival was calculated from date of detection and of curative treatment of the new malignancy and, therefore, was subject to the lead time bias.

Some critics may argue that our study was not a randomized trial in which one group of patients had follow-up and the other did not. The disadvantage of such a trial is that for reliable statistical analysis, thousands of patients are needed. How many patients can be found who willingly receive less long-term follow- up after treatment for a malignancy? After randomization, there still can be differences in the patient and tumor variables compared. The patients in the three groups in our study did not differ when compared on patient and tumor characteristics. Therefore, they could be compared on survival and mortality.

The reason for the current study was to take a critical look at the nationwide follow-up program for patients with laryngeal carcinoma in The Netherlands. Screening is conducted to reduce the cancer-specific mortality rate. However, a regular appointment system sometimes led to delay, because patients waited until the next prescheduled visit. In the de Visscher et al. 1994 study, this applied to 12% of the patients.[17]

In conclusion, our study did not show any survival benefit or reduced tumor mortality in the asymptomatic patient group. Therefore, the main aim of follow-up was not achieved. As the majority of tumor recurrences developed in the first 3 years of follow-up, the existing follow-up program might be too long. The other goals, such as management of complications and patient guidance, will always need some kind of follow-up program. However, the number of visits and the duration of follow-up need to be evaluated by more research into this topic. The definition of high risk patients and the provision of mental guidance by a specialized nurse can be taken into consideration.

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Chapter 3

Screening for second primary lung cancer after treatment of laryngeal cancer

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Abstract

Objectives/hypothesis.
As a result of smoking, patients who have received curative treatment for laryngeal cancer run a high risk of developing lung cancer. Therefore, these patients enter a screening program that aims to detect lung cancer at an asymptomatic stage. The study evaluated whether screening for lung cancer by means of regular chest x-ray examinations contributed to prolonging survival.

Study design.
A longitudinal follow-up study was performed to analyze the survival of patients who had received curative treatment for squamous cell laryngeal cancer and developed lung cancer during the follow-up period.

Methods.
Patients with lung cancer were divided into two groups: 1) patients with asymptomatic screen-detected lung cancer and 2) patients with complaints indicating lung cancer, whose tumor was detected in the interval between screening examinations by chest x-ray films.

Results.
In the complete group of patients with laryngeal cancer, no prognostic factors could be identified for developing lung cancer. There was no prolongation of survival in the screen-detected asymptomatic lung cancer patients. The median survival of both groups was 56 months (P = 0.57). The date of detection of the lung cancer was clearly brought forward by screening; a difference of 8 months was found between the median detection date of the two groups (P = <0.001). There was no difference in tumor specific mortality between the two groups.

Conclusion.
Screening by chest x-ray examination to detect lung cancer in an asymptomatic stage after curative treatment for squamous cell laryngeal cancer does not improve survival for patients who develop lung cancer.

Introduction

Several studies have been performed to evaluate the benefit of routine follow-up after curative treatment for head and neck or laryngeal cancer.[1–5] Routine follow-up is aimed at the early and presymptomatic detection of local recurrence, metastases, or second primary cancer, assuming that detection at an asymptomatic and therefore early stage enables curative treatment and improves survival.

Because of the common etiological factor of smoking, patients with laryngeal cancer run an especially high risk of developing lung cancer.[6–8] The incidence of lung cancer after treatment for laryngeal cancer varies between 2.8% and 11.2%.[9–11] Some studies have found that most second primary lung cancers developed in the first few years of follow-up, whereas other studies have reported a constant rate up to 10 years after curative treatment for laryngeal cancer.[4,7,8,12,13] Supraglottic laryngeal cancer seems to be associated with a higher incidence of lung cancer than glottic laryngeal cancer, and some authors have observed a higher incidence in men.[7,8,10,11,13] Because of improved therapy for laryngeal cancer, development of a lung tumor has become an important factor in the long-term survival, especially in early-staged laryngeal cancer.[6,7] Therefore, patients curatively treated for laryngeal cancer at most centers in the Netherlands enter a lung cancer screening program.

In 1992, a retrospective longitudinal study was published by Engelen et al. on the effect of screening for second primary lung cancer in patients treated in our clinic.[11] The median survival between the patients with a screen-detected asymptomatic lung malignancy (second primary cancer and lung metastases together) and patients with symptomatic lung malignancies differed with 6 months in favor of the first group. However, after stratification for the lead-time bias this survival benefit seemed to disappear. Lead-time bias means that by bringing forward the detection date the impression is given of postponing the date of death and prolonging survival.[14] Stalpers et al. in 1989 and Buwalda et al. in 1999 also showed survival benefit for patients with screendetected asymptomatic lung tumors after curative treatment for oral or laryngeal cancer by performing a chest x-ray examination every year during the first 5 years of follow-up.[15,16] However, the authors suggested that the biological behavior of lung tumors detected by routine chest x-ray examinations is different (less aggressive and slower growing) from that of symptomatic lung tumors. Therefore, prolongation of survival is not caused by the early detection but by the fact that tumors with slow growth are detected by

the routine chest x-ray examination. This phenomenon is called the "length bias."[17,18]

Based on the results of the studies by Engelen et al. and Stalpers et al. (i.e., that most lung tumors developed in the first 2 years of follow-up), the screening program for all patients with head and neck cancer in our institute was altered.[11,15] The frequency of screening chest x-ray examinations was intensified. During the first 2 years of follow-up, chest x-ray examinations were made once every 6 months instead of once every year. In the new follow-up screening program, in all, seven screening x-ray films of the chest were made over a period of 5 years. However, in some patients the yearly performance of routine x-ray examination once a year was continued after the fifth year of follow-up if the patient insisted.

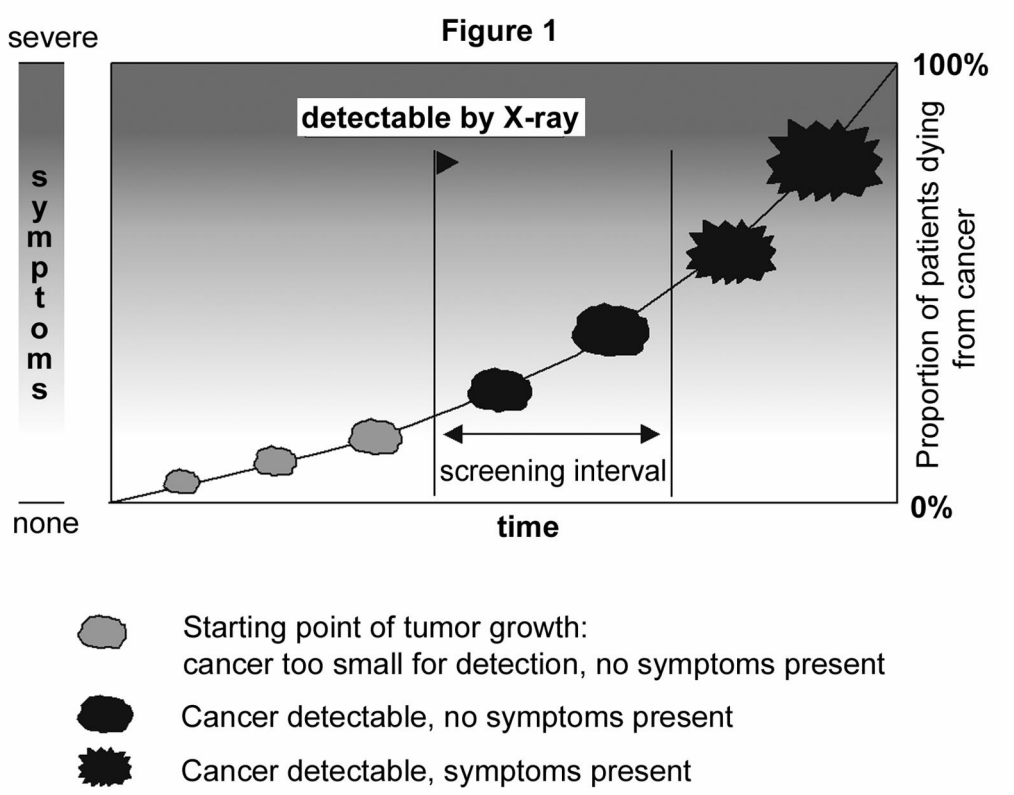

Figure 1. Graph representing a hypothetical natural course of lung cancer from onset towards the time that cancer can be diagnosed by chest radiography, towards the time that a tumor gives rise to symptoms and eventually evolving towards the time of death from a fatal volume.

The basic principles of the screening program are explained in Figure 1. The tumor load increases in time and determines cancer-related survival. It is assumed that symptomatic carcinomas are in a more advanced stage than asymptomatic carcinomas. When a single patient develops lung cancer during the follow-up

program, at first, it is too small to be detected radiologically. The tumor increases in volume, and at a certain point the lung tumor is detectable, although still in an asymptomatic stage. After some time, symptoms occur, and in this stage the chance of being cured is less compared with the asymptomatic stage. The proportion of patients dying of lung cancer is higher in the symptomatic stage compared with the asymptomatic stage. The purpose of the routine x-ray examinations is to detect the patients with lung cancer before development of symptoms. The main purpose of the present study was to evaluate whether the new screening protocol with an increased number of chest x-ray examinations led to improvement of survival for patients curatively treated for squamous cell laryngeal carcinoma who developed lung cancer.

Patients and methods

The study group comprised all consecutive patients with primary squamous cell carcinoma of the larynx who were referred to our Head and Neck Oncology Group between January 1988 and January 1993 and had received curative treatment. Exclusion criteria were a history of head and neck or lung cancer or a lung tumor present at the time of detection of the laryngeal carcinoma. Patients cured of other malignancies were eligible because the main purpose of the screening was to detect primary lung cancer.

All laryngeal tumors were staged according to the Union Internationale Contre le Cancer TNM classification of 1987 by tumor site. The treatment for T1 and T2 glottic carcinomas consisted primarily of radiotherapy (66–70 Gy in daily fractions of 2 Gy), leaving surgery available for salvage therapy. Treatment of first choice for T3 and T4 glottic carcinomas was a total laryngectomy followed by radiotherapy in the case of incomplete removal of the laryngeal tumor and/or invasion of cartilage or soft tissues of the neck. Small supraglottic T1, T2, and some T3 tumors were treated with irradiation or, when this was not possible, surgically by performing a partial laryngectomy, followed by postoperative radiotherapy when indicated. Patients with T3 and T4 tumors underwent a total laryngectomy. Treatment for patients with regional metastases from the laryngeal tumor comprised irradiation of the neck if the tumor had been treated by irradiation. A neck dissection was performed when the tumor had been treated surgically, and this was followed by radiotherapy in the case of capsular disruption or multiple positive lymph nodes.

Patients were offered a follow-up schedule of 17 routine visits in 5 years with a decreasing frequency. The intervals between routine visits were 2 months in the first year of follow-up, 3 months in the second year, 4 months in the third year, and 6 months the fourth and the fifth years. After 5 years of follow-up most patients were no longer followed by the Head and Neck Oncology Group but were advised to be seen once a year up to 10 years of follow-up by an otorhinolaryngologist near their home. On these routine visits the chest x-ray examinations were planned as described earlier.

A lung malignancy was classified as second primary cancer when it differed histologically from the laryngeal tumor. In case of a squamous cell carcinoma, the histological criteria for second primary tumors according to Warren and Gates, modified later by Gluckman et al., had to be met.[19,20] In some patients, no tissue specimen was available for histological confirmation because of severe comorbidity or the patient's wishes. The malignancies in these patients were considered to be second primary lung cancer if they concerned a solitary tumor without lymph node metastases and there were no signs of local or regional recurrences or other tumor activity at the time of detection.

To answer the study question, the patients who developed lung cancer were divided into two groups: 1) patients with asymptomatic lung cancer, which was screen-detected, and 2) patients with symptomatic lung cancer that was detected on an extra chest x-ray film made in the interval between the routine screening chest x-ray examinations, based on specific complaints.

Survival curves were calculated and compared for these two groups. First, this was performed using the date of detection of the primary lung cancer (the date of the positive chest x-ray film); second, the overall survival was calculated from the date that the laryngeal carcinoma was histologically confirmed. Also, the tumor specific mortality was calculated and compared.

Survival analyses were performed using the Kaplan-Meier approach, and the log rank test was used to compare the two groups. Probability to develop second primary lung cancer based on patient or tumor characteristics was calculated using nonparametric statistics (Fisher's Exact test).

Results

The records of 502 patients were studied, and 476 patients could be included; 26 patients did not meet the inclusion criteria. Follow-up closed in February 2000. The median follow-up period was 51.8 months. Only a few patients were still followed

in our department after the first 5 years of follow-up. There were 2008 x-ray films of the chest (routine and extra) made during the follow-up of the complete group.
Of the study group of 476 patients, 430 (90.3%) were men and 46 (9.7%) were women. Distributed by age, we found 10 patients (2.1%) younger than 40 years of age. In all, 46 patients (9.7%) were between 40 and 50, 125 patients (26.2%) were between 50 and 60, 147 patients (30.9%) were between 60 and 70, 106 patients (22.3%) were between 70 and 80, and 42 patients (8.8%) were older than 80 years of age. Table 1 shows the distribution by laryngeal cancer site and TNM stage. Most glottic tumors were stage I or II (83.7%), and most supraglottic tumors were in a more advanced stage (stage III or IV) (64.2%). The 5-year survival rate of all patients was 74%. After treatment of the laryngeal carcinoma and during follow-up a total of 48 (10.1%) patients developed lung metastases or a second primary cancer in the lungs, 46 men (10.7%) and 2 women (4.2%). Of all patients with lung cancer together after 2 and 3 years of follow-up, respectively, 14% and 11% were alive. The median survival was 9 months.

Table 1. Distribution by tumor site and UICC stage of the 476 patients.

Site/stage	I	II	III	IV	Total
Supraglottic	20	43	49	64	176
Glottic	150	96	29	19	294
Subglottic	1	3	0	2	6
Total	171	142	78	85	476

Second Primary Lung Cancer

In 25 patients (52.1% of all lung tumors) the lung tumor was classified as primary lung cancer. In 19 cases this was histologically proved. Of these 19 patients, 11 (57.9%) had squamous cell lung cancer, 4 patients had an adenocarcinoma, and the remaining 4 lung carcinomas were histological types such as small cell lung carcinoma and carcinosarcoma. In case of a squamous cell lung cancer, the criteria of second primary lung cancer according to Warren and Gates, modified by Gluckman et al., were applied.[19,20] In six patients, no specimen for histological confirmation could be obtained but these tumors were considered to be primary lung cancers according to the criteria described in “Patients and Methods.” Of the primary lung cancers, only four cases (16%) occurred in the first 2 years of follow-up. After 5 years of follow-up another eight cases (32%) of the lung cancer were detected. Figure 2 specifies exactly when the lung carcinoma or lung metastases

were detected during the follow-up. In the first 3 years the number of lung metastases is notably higher compared with the following years, whereas the incidence of patients with primary lung cancer shows a more constant rate during the follow-up period.

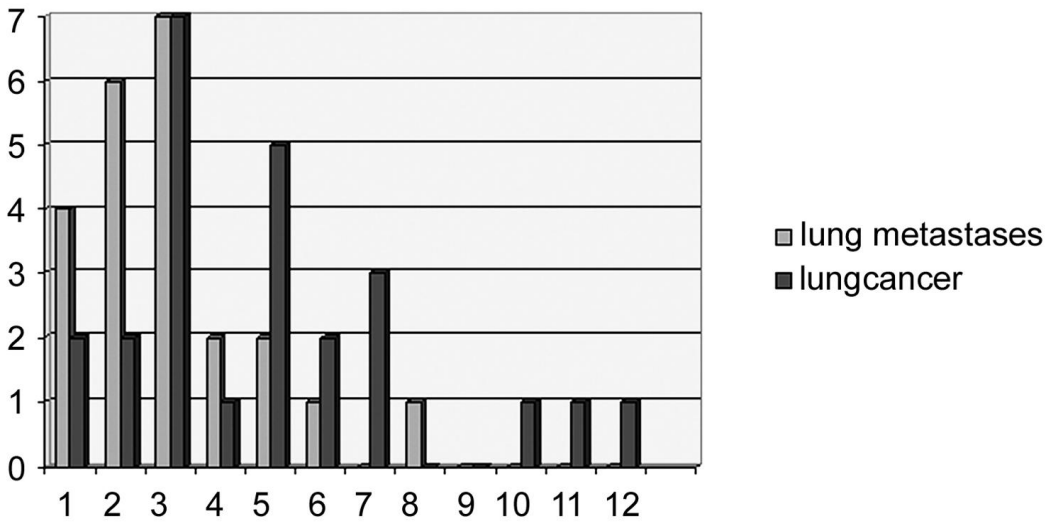

Figure 2. Year of detection of lung cancer during the follow-up periode.

No significant difference in the probability of developing primary lung cancer according to gender was found. Grouping the laryngeal tumor by histological type (well, moderately, or poorly differentiated carcinoma in situ or squamous cell carcinoma not classified), again, no significant difference in development of lung cancer could be demonstrated. In addition, the N stage of the primary laryngeal tumor did not show an influence on the lung carcinoma development. We could not find a higher incidence of lung cancers after the supraglottic laryngeal cancer compared with the glottic laryngeal carcinoma, and there was no difference in time of development ($P = 0.72$).

Table 2 shows the different characteristics and lung cancer development.
A comparison was made between the histological types of the second primary lung cancer and presence of symptoms at the moment of detection. There seemed to be a relation between presence of complaints and the possibility that the lung cancer is a squamous cell carcinoma ($P = 0.059$) (Table 3).

Table 2. Patients and laryngeal cancer characteristics in the development of second primary lung cancer.

Characteristics	Patients	476	Second primary lung cancer (25)	Percentage second primary lung cancer
Sex	Male	430	24	5.6
	Female	46	1	2.2
Localization	Supraglottic	176	10	5.7
	Glottic	294	14	4.8
	Subglottic*	6	1	-
Histology	CIS	10	2	-
	Well differentiated	84	4	4.8
	Moderately	316	15	4.7
	Poor	64	4	6.25
	Squamous-cell ca-unspecified	2	0	-
TNM stage	I	171	6	3.5
	II	142	9	6.3
	III	78	3	3.8
	IV	85	7	8.2
N-stage	N0	401	21	5.2
	N+	75	4	5.3

No statistical difference in lung cancer rates.
* Not included in analyses.

Table 3. Second primary lung cancer (histologically proven, n = 19), classified by histology and complaints (no stratification for type of visit; extra or routinely).

Complaints/histology	Squamous cell	Different	Total
No complaints	4	7*	11
Complaints	7	1†	8
Total	11	8	19

* Four patients had an adenocarcinoma 3 patients had other types of lung cancers.
† This patient had two lung malignancies, the first was a carcinosarcoma and the second was a squamous-cell carcinoma.

Survival

The two groups as described earlier, divided by mode of presentation (no complaints, routine visit/complaints extra visit), were analyzed separately, and the

survival curves were compared. The group of patients in which the screening program was successful because the lung carcinoma was detected in an asymptomatic stage contained 14 patients. The group of patients with symptoms contained seven individuals. The two patients with complaints of their lung malignancies that were found on a routine visit were excluded from analysis. These patients obviously have had no benefit from the screening program and might even have waited with their complaints until the prescheduled visit at the physician's office. Also, the two patients without complaints of their lung malignancies that were detected on an extra visit were excluded. These patients had had an x-ray examination of the chest for other reasons. They did not fit in the group of patients who have had benefit from the screenings program, nor did they fit in the group of patients with complaints.

Survival curves for both groups (asymptomatic/routine control and symptomatic/ extra control) were calculated starting at the date of detection of the lung cancer, resulting in a highly significant difference between the two groups (P = 0.001) (Figure 3).

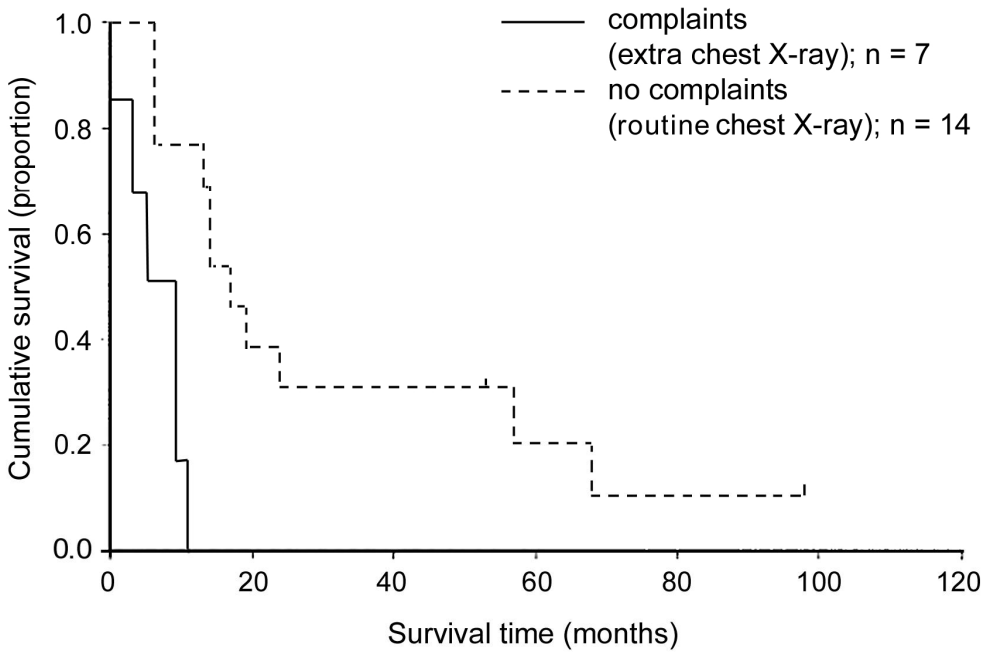

Figure 3. Survival of patients with second primary lung cancer (calculated from date of positive findings on chest x-ray examination).

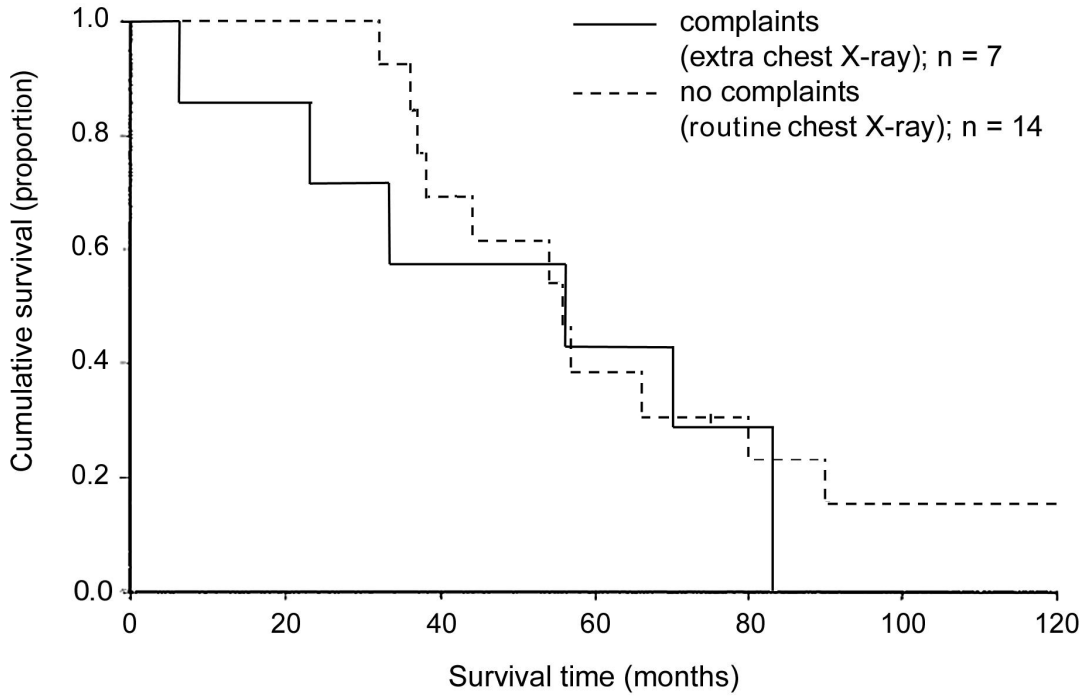

Figure 4. Survival of patients with second primary lung cancer (calculated from date of detection of laryngeal cancer).

The median survival of the presymptomatic/routine group was 17 months, and for the symptomatic/extra control group, 9 months. However, when the survival was calculated from the detection date of the primary laryngeal tumor, no difference in survival was found (P = 0.57) (Figure 4). The median survival of both groups was exactly the same (56 mo). The percentage of patients who had surgery did not differ between the two groups. The treatment options for the two different groups are summarized in Table 4. The tumor-specific mortality was calculated and compared between the two groups. In the asymptomatic/routine group, 8 of 14 patients were treated with curative intent. Ultimately, two patients were alive and free of disease at the end of the follow-up period. Five patients died of cancer; in one patient the cause of death could not be found. In the symptomatic/extra control group, three of seven patients were treated with curative intent and all three died before the end of the follow-up period. Two died of cancer (metastases), and in this group the cause of death in one patient could not be found. Tumor-specific mortality neither calculated from date of detection of the lung carcinoma nor calculated from detection of the laryngeal cancer showed a statistically significant difference between the two groups (P = 0.32 and P = 0.61). Please note that the groups of comparison are small.

Table 4. Distribution of second primary lung cancer by mode of detection and treatment

Detection mode	Second primary cancer	Number of patients operated on (%)	Number of patients treated with radiotherapy (%)
Screen-detected	14	*6/14 (42.9)	2/14 (14.3)
By complaints	7	3/7 (42.9)	0/7 (0)
Total	21**	9/21 (42.9)	2/21 (9.5)

*1 patient received radiotherapy combined with surgery.
**The total amount of second primary lung carcinomas is 25, but 4 patients were excluded since they did not fit the two patient groups compared.

Lung Metastases

The purpose of the follow-up screening program is mainly to discover primary lung cancer, but also lung metastases are detected. Because nearly half (47.9%) of the detected lung tumors are thought to be lung metastases of the previously treated laryngeal cancer, details are given. Most lung tumors detected in the first 2 years of follow-up are metastases of the primary laryngeal cancer (Figure 2). Of the patients with lung metastases, 7 had specific complaints and 16 were complaint free. Whether or not the lung metastases were detected in the routine program was of no interest; therefore, no correction was made for the type of chest x-ray examination made (routinely or extra based on complaints) as was made for the second primary lung cancers. Both survival curves calculated from the date of detection of the metastases ($P = 0.84$) and those calculated from detection date of the primary laryngeal cancer ($P = 0.19$) showed no statistical difference in survival.

Discussion

To detect second primary lung cancer in an early stage, routine x-ray examinations of the chest are made during the follow-up screening program after cure of laryngeal cancer. There is doubt as to whether this screening contributes to a better survival in patients who develop lung cancer.

In the present study, only 11 of 25 patients with lung cancer could be offered treatment with curative intent. Of all patients treated for their lung malignancy with curative intent, only three patients were still alive at the end of the follow-up period. In all three patients the follow-up period after lung cancer detection was more than

5 years. One of these patients had complaints but the lung cancer was detected on a prescheduled x-ray examination of the chest; the other two patients had presymptomatic screen-to detect lung cancer. Therefore, the screening program detected the lung malignancy in only two patients.

By increasing the number of routine x-ray examinations of the chest in the first 2 years of follow-up, we expected to detect more lung tumors in an asymptomatic stage leading to treatment of more patients with curative intent and thereby increasing the survival of patients who developed lung cancer. Our results clearly show that the majority of lung tumors detected in the first 2 years of follow-up are lung metastases. It is not to be expected that the increase in x-ray performance in the first 2 years has led to detection of more primary lung cancers in an asymptomatic stage. The inclusion of lung metastases in the previous studies might have led to the high detection rate in these years of follow-up.[11,15] Our results show a steady incidence of primary lung cancer after the first 2 years of follow-up with a peak incidence in the third year (Figure 2). The development of second primary lung cancer is not limited to the first 5 years of the follow-up program. One third of all second primary lung malignancies were detected after the fifth year of follow-up.

No risk factors related to the laryngeal tumor were found that indicated a higher chance of developing primary lung cancer. We did not find a higher incidence in men.

No higher rate of primary lung cancer following supraglottic laryngeal cancer compared with glottic laryngeal cancer was found. This is not consistent with the literature.[7,8,11] Wagenfeld et al.[7,8] found a higher incidence of primary tumors of the respiratory tract after supraglottic laryngeal cancer (19% after supraglottic laryngeal cancer and 6.5% after glottic laryngeal cancer). After comparison of the number of lung tumors instead of all respiratory tract tumors the difference remains but is reduced to 7.9% following supraglottic laryngeal cancer and 3.3% after glottic laryngeal cancer. In the study by Engelen et al., primary lung cancer was not analyzed separately but was grouped together with lung metastases.[11] Supraglottic laryngeal cancer is in a less favorable stage when detected compared with glottic laryngeal cancer. It could well be that the higher incidence of lung tumors found in the patients with supraglottic laryngeal cancer in the previous study is mainly due to a higher incidence of lung metastases.

As stated earlier, nearly all lung cancers causing complaints were squamous cell carcinomas and nearly all other histological types were in an asymptomatic stage when detected. A possible explanation is that squamous cell carcinomas more often develop in the central portion of the bronchi, whereas adenocarcinomas

develop predominantly in the peripheral portion. Therefore, the presence of symptoms could be explained by different histological appearance and different biological behavior of the lung tumor and does not imply a less favorable survival outcome. However, it must be said that Buwalda et al. did not find more squamous cell carcinomas in the symptomatic group.[16]

Compared with patients with complaints indicating lung cancer, the survival of patients with second primary lung cancer, calculated from the date of the positive x-ray examination of the chest made during the screening program, differs by 8 months. The survival calculated from the date of detection of the laryngeal tumor revealed no difference between the groups compared. The comparison of survival from the time of diagnoses, because of lead-time bias and length bias, can be misleading. In our opinion, the date of death was not altered by discovery of the second primary lung cancer in an asymptomatic stage; rather, the date of detection of the lung cancer has merely been put forward by the screening program. The best way to measure the effect is by comparison of the disease specific mortality. In the present study no difference was found between the asymptomatic and symptomatic groups.[21]

We cannot say anything about the benefit of computed tomography (CT) screening for second primary lung cancer. Recently, it has been reported that screening for lung cancer in high-risk groups by means of CT imaging does lead to a higher rate of detection of lung tumors when they are smaller compared with screening by means of chest x-ray examinations.[22] The detection of lung cancer when the tumor is as small as possible does have a positive impact on survival.[23] However, even by the time the tumor is visible on CT, it already may have spread. Furthermore, many tumors that are not clinically relevant may be discovered in this way.[21] It has to be taken in consideration that the screening program for lung cancer in these studies was performed in patients who had no history of cancer and were fit to undergo thoracic surgery. Furthermore, the incidence of developing lung cancer in their group varied between 10% and 12%, and the chance of developing lung cancer following laryngeal cancer was only 5.3% in our study.

Conclusion

To detect 8 patients with an asymptomatic, routinely found second primary lung carcinoma, which could be treated with curative intent, and to eventually cure 3 of a group of 476 high-risk patients, 2008 (routine and additional) x-ray examinations of the chest were made. The percentage of patients developing second primary

lung cancer after treatment for laryngeal cancer with a median follow-up time of 51.8 months was 5.3%. Despite the many years of screening for lung cancer in our clinic, involving the effort of both patient and doctor, there is no difference in survival or disease-specific mortality for patients with or without symptoms of their lung malignancies. The intensified screening program by increased controls with regular chest x-ray examinations in the first 2 years of follow-up only resulted in putting forward the date of detection. Because of the screening program, it is probable that malignancies which ultimately have no influence on the well being or mortality of the patient, early detection of cancer which is not curable, and maybe even patient-delay of patients with symptoms will have occurred. Up until the present, the sole reason for performance of this screening program has been the high risk of developing lung cancer in the laryngeal cancer population. Duration of the program and the number of chest x-ray examinations to be scheduled are missing any good argumentation. The survival of patients who develop second primary cancer in the lungs seems to be determined more by the biological behavior of the tumor and the presence of co-morbidity than by the mode of detection. Confronted with the disappointing results, we conclude that there is no reason for extending the screening program using routine chest x-ray examinations.

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Chapter 4

Cancer recurrence after total laryngectomy: treatment options, survival and complications

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Abstract

Background.
A follow-up schedule to detect asymptomatic cancer recurrence is offered to all patients with laryngeal cancer. In this study, the therapeutic options, prognosis, and morbidity of patients with total laryngectomy who were found to have cancer recurrence during this follow-up schedule were determined.

Methods.
Patients who had undergone a total laryngectomy between January 1, 1990, and January 1, 2000, and had cancer recurrence were included. Data from this group were analyzed retrospectively.

Results.
The prognosis was poor after the development of cancer recurrence. Curative therapy could only be offered to 27.5% of these patients. Only 5% of the patients were disease free at the end of the study period. Many patients with cancer recurrence needed interventions. A large proportion of them had complications.

Conclusions.
The follow-up schedule offered to patients after total laryngectomy should put greater emphasis on care than on early detection of cancer recurrence.

Introduction

All patients treated with curative intent for laryngeal cancer in The Netherlands are offered a routine follow-up schedule in accordance with the national guideline.[1] This includes 22 routine visits over a period of 10 consecutive years, with decreasing frequency as time progresses. In the first year of follow-up, the patient has a routine visit every 2 months (six times a year). In the second year, the patient is seen every 3 months (four times a year); in the third year, every 4 months (three times a year); in the fourth and fifth years, twice a year; and thereafter up to 10 years, once a year. During the follow-up period, patients are free to visit the clinic in between if they have complaints. At each visit (prescheduled and extra), an interview was performed, as well as a complete physical examination of the head and neck. In case of performance of a total laryngectomy, this schedule was also conducted.

The main purpose of this schedule is the early detection of asymptomatic local and/or regional failure on the assumption that this will lead to better survival and reduction of treatment-related morbidity. However, in patients with local or regional recurrence after total laryngectomy, the question arises what options are left for treatment with curative intent. There may not be any advantage in offering these patients the same strict and intensive follow-up schedule as in those treated with larynx preservation.[2]

There is a long tradition of treatment of patients with laryngeal cancer at the Radboud University Nijmegen Medical Centre. Recently, data from these patients on treatment, cancer relapse, cancer-specific mortality, and survival have been evaluated in relation to the follow-up criteria.[2,3]

The treatment applied to the patients with T1 or T2 glottic carcinomas during the study period was primarily radiotherapy (64–70 Gy in daily fractions of 2 Gy), leaving surgery available for salvage therapy. Only a few patients with a small glottic carcinoma underwent (CO2) surgery of the vocal cords. This therapy was also reserved for patients with carcinoma in situ. Small supraglottic T1, T2, and some T3 tumors were treated with radiotherapy, including elective irradiation of the neck or, when patients fulfilled certain strict criteria, surgery that was made up of partial laryngectomy followed by postoperative radiotherapy when indicated. Treatment for T3 and T4 glottic carcinomas and T3 and T4 supraglottic tumors was, if possible, radiotherapy or a total laryngectomy followed by radiotherapy in the case of incomplete removal of the tumor and/ or invasion of cartilage or soft tissues of the neck. Patients with regional metastases from the laryngeal tumor received radiotherapy to the neck if the primary tumor was treated with

radiotherapy. A neck dissection was performed when the primary tumor was treated surgically, followed by radiotherapy in the case of capsular disruption or multiple positive lymph nodes.

In patients treated for cancer, not only lifeyears gained are important but also the quality of life in those years.[4] The routine follow-up schedule aims to detect asymptomatic cancer relapse on the assumption that asymptomatic patients will have less advanced disease; therefore, there will be more therapeutic options left, resulting in an improvement of prognosis. In this study, we determined the localization and extent of the cancer recurrence that patients with total laryngectomy had. We also determined the therapeutic options left, morbidity, and prognosis. In addition, the adverse events, which our patients had after treatment of cancer recurrence, were scored.

Patients and methods

A longitudinal study was performed on all the patients who had undergone total laryngectomy with curative intent in our center, either for primary treatment of squamous cell laryngeal carcinoma or for salvage therapy in the case of local recurrence after radiotherapy between January 1, 1990, and January 1, 2000. A total of 259 patients were included. During the study period, which ended at January 1, 2001, 80 of these 259 patients had cancer recurrence. The medical records of these 80 patients were reviewed to document the date of cancer detection during follow-up, date of treatment and treatment modality of the cancer recurrence, date of death, and cause of death after the detection of cancer recurrence. Cancer recurrence was defined as local or regional cancer recurrence, metastases, or second primary tumors.

Second primary tumors were localized in the upper aerodigestive tract or elsewhere in the body. Second primary tumors of the skin were not found in our study population. Complications and interventions were scored, as well as the intake of food and the preferred method of speech. Other events, such as psychiatric complications, were also documented.

Patient data were entered into a database (Access). Survival analysis was performed using the Kaplan–Meier method. The log-rank test was used to calculate differences between survival curves.

Results

Population

A total of 259 patients had undergone a total laryngectomy for primary or local recurrence of squamous cell carcinoma between January 1, 1990, and January 1, 2000. Cancer relapse after total laryngectomy was detected in 80 of these 259 patients, 70 men and 10 women. The mean age of these 80 patients was 61.9 years (range, 38.5–85.4 years) at the time of diagnosis of the initial laryngeal tumor. Most of these 80 patients had been treated for primary glottic cancer (n = 44), whereas 29 patients had been treated for supraglottic cancer; seven patients had subglottic cancer. Stage I primary laryngeal tumor had been diagnosed in 11 patients, stage II in 17 patients, stage III in 13 patients, and stage IV in 39 patients (Union Internationale Contre le Cancer, fifth edition 1997). Histologic classification showed that 34 patients had poorly differentiated squamous cell carcinoma, 40 had moderately differentiated carcinoma, and only four had well-differentiated carcinoma. In two patients, there was no record of the degree of differentiation of the squamous cell carcinoma. The pretreatment lymph node status was N0 in 53 patients and N+ in 27 patients. Because the primary treatment had the intention to cure, no M+ patients were included in the study.

In the group of 80 patients who were found to have cancer relapse, only six patients had undergone a total laryngectomy for their primary tumor as a single treatment modality, whereas 32 patients had undergone a laryngectomy followed by postoperative radiotherapy. A group of 39 patients had initially been treated with radiotherapy. Three patients had a different therapy pathway. Table 1 summarizes the therapy pathway of all the patients.

Table 1. Overview of initial therapy pathway in 80 of 259 patients with laryngectomy who had cancer recurrence develop during follow-up.

Therapy	Number of patients (n=80)
Laryngectomy for primary tumor	6
Laryngectomy for primary tumor with postoperative radiotherapy	32
Radiotherapy for primary tumor, laryngectomy for recurrence	36
Radiotherapy for primary tumor, laryngectomy+radiotherapy for recurrence	3
Chordectomy for primary tumor, laryngectomy for recurrence	1
Other	2

Cancer Recurrence

The mean interval between total laryngectomy and the detection of cancer recurrence was 11.6 months. Fifty percent of the recurrences after total laryngectomy were detected within 8.8 months of follow-up, more than 90% of all recurrences were diagnosed within 2 years of the follow-up (Figure 1). Two patient groups could be distinguished: patients with symptomatic recurrence (n = 58) and patients in whom asymptomatic recurrence had been detected (n = 16). In six patients, it was not clear whether they have had cancer-specific complaints. There was no significant difference in the interval until recurrence detection between the two groups: 12.4 months and 10.4 months, respectively (*P* = 0.69). Also, no difference was found in the disease-free interval between the patients who had undergone primary or salvage laryngectomy (*P* = 0.35).

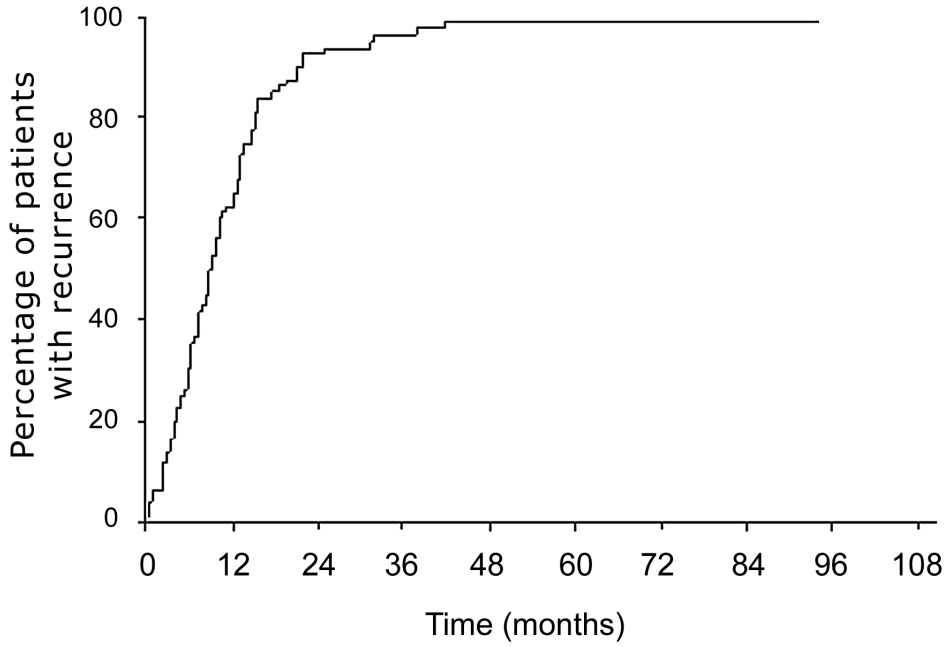

Figure 1. Time from total laryngectomy to cancer recurrence (*n* = 80).

No statistical difference was found in time until the three different types of cancer recurrence developed (*P* = 0.09). The mean interval until local/ regional failure (n = 49) was 12.3 months; second primary cancer (n = 10), 6.6 months; and metastases (n = 20), 13.2 months. Second primary tumors seemed to develop earlier in time during the follow-up period after laryngectomy than local/ regional cancer recurrence or distant metastases. Please note that only three of 10 second primary tumors were situated in the head and neck region. Most of the second primary tumors were lung carcinomas (n = 5) or other tumors (n = 2). Table 2 shows the site and type of cancer recurrence.

Table 2. Localization and type of cancer recurrence in 80 of 259 patients after laryngectomy.

Localization and type of cancer recurrence	No. of patients with recurrence (%) (*n* = 80)
Tracheostomal recurrence	10 (12.5)
Neopharynx	8 (10)
Lymph node in the neck	28 (35)
Skin of the neck	3 (3.8)
Second primary	
Head and neck	3 (3.8)
Lung	5 (6.3)
Elsewhere	2 (2.5)
Lung metastases	13 (16.3)
Metastases elsewhere	7 (8.8)
Residual tumor after treatment	1 (1.3)

Therapy

Twenty-two patients (27.5%) with cancer recurrence could be treated with curative intent. Fifteen of these patients had local/regional cancer recurrence, and five patients had a second primary tumor. Most of these patients received surgery combined with radiotherapy (n = 9); eight patients received surgery alone. The rest of the 22 patients were treated with curative intent with radiotherapy, or radiotherapy/surgery combined with chemotherapy. Thirty patients with cancer recurrence (37.5%) received palliative treatment. Eighteen patients received radiotherapy; 10 patients, chemotherapy; one patient, chemotherapy combined with radiotherapy; and one patient, surgery combined with chemotherapy. No therapy but supportive care was applied in 26 patients (32.5%). In 16 of these 26 patients, treatment was not possible because of medical reasons, such as the tumor was inoperable, the maximal dose of radiotherapy already had been applied, or the comorbidity of the patient was too severe to receive any form of treatment. Nine patients refused therapy; in one patient the reason was unknown. Table 3 shows the overall therapy applied to the 80 patients.

Survival

Mean survival in the patients who had cancer recurrence after total laryngectomy was 24.8 months from the date of the laryngectomy; the median survival was 16.6 months (Figure 2).

There was no difference in survival between the patients who initially were seen with symptoms or without symptoms of their cancer recurrence (*P* = 0.15): mean survival was 22.8 months and 28.6 months, respectively. No difference in survival was found between the patients who had undergone primary total laryngectomy

and those who had undergone laryngectomy as salvage therapy and had cancer recurrence (*P* = 0.57). The survival of the patients with local or regional failure, a second primary tumor, or distant metastases did not show any difference (*P* = 0.38).

Table 3. Treatment modalities for local and regional cancer recurrence, distant metastases, and second primary tumors.

Therapy	No. of patients (%) (*n* = 80)
Surgery	8 (10)
Radiotherapy	20 (25)
Surgery+radiotherapy	9 (11.25)
Chemotherapy	10 (12.5)
Chemotherapy + surgery	2 (2.5)
Chemotherapy + radiotherapy	2 (2.5)
No therapy	26 (32.5)
Unknown	3 (3.75)

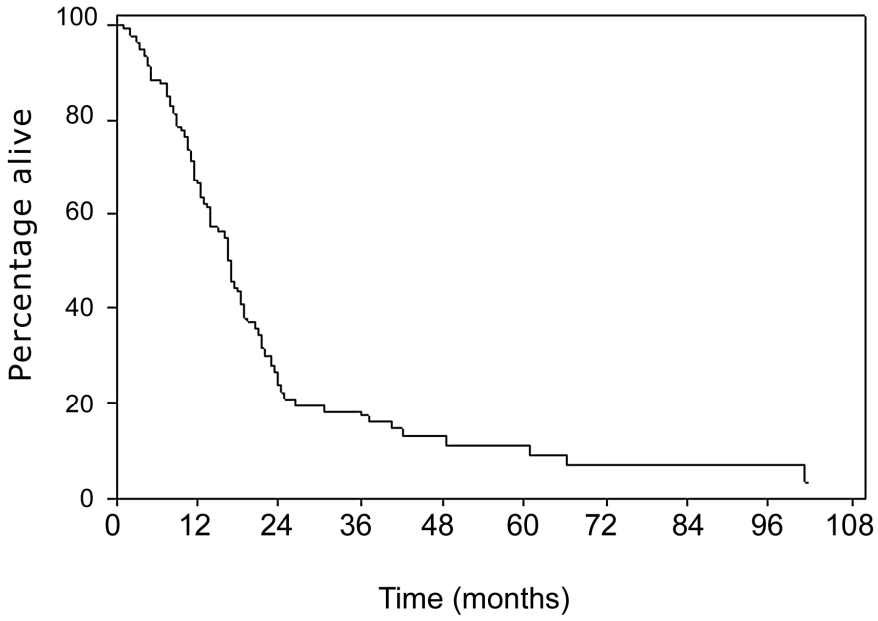

Figure 2. Overall survival from the date of total laryngectomy in patients with cancer recurrence (*n* = 80).

After the detection of cancer recurrence, mean survival was only 12.9 months. Fifty percent of the patients with cancer recurrence died within 5.4 months after detection. By the end of 2000, 71 of the 80 patients had died, and 65 (92%) of them died of the cancer recurrence. Of the nine survivors, only four patients were

disease free, and only one has had an asymptomatic tumor recurrence. None of the five patients who were alive at the end of the study period with disease could be offered any therapy with curative intent.

Calculated from the date of the total laryngectomy, mean survival in the patients treated with curative intent was 31.7 months. Mean survival in patients who had been treated palliatively or had not received treatment was 21.2 months (P = 0.03). Mean survival after recurrence detection in patients treated with curative intent was 22.4 months. Patients who had been treated with palliative intent or had not received any treatment had a mean survival of 7.7 months ($P < 0.001$).

Complications

Complications and interventions were scored in the study population after tumor recurrence had been detected. Hypothyroidism had developed in 14 patients (17.5%). Many of the patients had a fistula developed (n = 31). The most common types led from the pharynx outward to the skin and from the pharynx toward the trachea. At least 30% of the patients were initially seen with minor, but persistent, bleeding, mostly from the tracheostomy or around the fistula. One patient had this complication 10 times. Four patients died of a carotid blowout. Because of poor nutritional state, radiotherapy, tumor recurrence, or without clear cause, 15% of the patients had local infections developed. Table 4 shows the number of patients with a specific complication and the total number of specific complications.

Table 4. Complications after local or regional cancer recurrence, distant metastases, and second primary tumors until death.

Complication	No. of patients affected (n = 80)	Frequency of complications in 80 patients
Fistula	31	36*
Minor bleeding	24	50*
Pneumonia	9	10*
Wound infection	12	12
Disruption of wound edges	3	3
Rupture of carotid artery	4	4
Nervous phrenicus paralysis	2	2
Clinical treatment of pain	6	6
Hypothyroidism	14	14
Total no.		137 complications in 80 patients

*Complication sometimes occurred more than once in the same patient.

Interventions

The number of interventions and investigations caused by complications after tumor recurrence, or for diagnostic purposes, was also scored. Placement of a laryngectomy tube to secure the airway (eg, in the case of obstruction because of crust formation or tumor growth) had been necessary in 31% of the patients. Table 5 shows the other types of interventions and the number of patients undergoing them.

Table 5. Frequency of interventions after cancer recurrence.

Intervention	No. of patients	No. of interventions
Esophagoscopy	12	15
Bronchoscopy	7	8
Dilatation of the neopharynx	9	16
Placement of tube in tracheostoma	25	45
Cleavage of pseudovallecula	4	4
Total no.		88 interventions in 80 patients

After total laryngectomy, patients were trained to speak with the use of a tracheoesophageal voice prosthesis. This was successful in most of the patients (n = 59; 74%). After the development of cancer recurrence, this type of speech was possible in only 20 patients (25%). Before the cancer recurrence, three patients used esophageal speech; this was reduced to only one patient still using this type of speech method after the treatment for cancer recurrence. Two patients used the electrolaryngeal speech method, 13 patients (16%) after treatment for cancer recurrence. Three patients had no satisfactory speech method after the total laryngectomy; after treatment of the cancer recurrence, this was the case for six patients.

In our study group, 10 patients had a depression or needed other psychiatric help after the detection of cancer recurrence. Eight patients had been admitted to a hospital or nursing home on social indications. All the interventions and complications after the development of cancer recurrence resulted in 120 hospital admissions for 60 patients.

Discussion

Patients who have cancer recurrence after total laryngectomy for laryngeal cancer do not have many treatment options left, particularly not when radiotherapy already has been applied. The most important aim of regular follow-up visits after treatment for laryngeal cancer is the early detection of asymptomatic local or regional failure on the assumption that this will result in a better survival outcome and less treatment-related morbidity. It is known that prognosis is related to the stage of the primary tumor and, therefore, to early tumor detection. Screening programs that focused on breast cancer and colon carcinoma, for example, showed better survival outcome in this respect. However, it is questionable whether this is true for cancer recurrence after radical treatment for advanced-stage cancer.[5,6] In our opinion, the intensity of the therapy applied to the primary laryngeal tumor, the tumor stage, comorbidity, and age of the patient should be considered before offering a frequent and long-term follow-up program.

From January 1, 1990, until January 1, 2000, 259 patients were treated for primary laryngeal squamous cell carcinoma or for laryngeal cancer recurrence by performance of a total laryngectomy. A total of 80 patients had cancer recurrence in the period from January 1, 1990, until January 1, 2001. Cancer relapse in the head and neck region (recurrence and second primary tumors) was detected in 49 of these 80 patients. The mean disease-free interval in this group was only approximately 1 year. Curative treatment could be offered to 22 patients (27.5%) but was successful in only four patients (according to the definition of disease-free survival at the end of the study period).

Despite the effort of the follow-up program, there were no curative therapeutic options left for most of patients who had cancer recurrence after total laryngectomy. The patients who received therapy with intention to cure (n = 22) had a better survival outcome than the patients who did not receive any therapy and those who received palliative therapy. This is consistent with observations by Yuen et al.[7] However, on the basis of our own results, we disagree with the conclusion that early detection led to improved survival. Better survival outcomes could be attributed to the type of tumor recurrence, absent comorbidity, and the availability of further therapeutic options instead of asymptomatic detection during the follow- up program.[8] Spector et al described that the chance of distant metastases developing was higher in the patients who were initially seen with advanced-stage (T4) primary disease.[9] Because of better local and regional control of the primary malignancy, it is more likely that these patients will die of distant metastases, because distant metastases from squamous cell laryngeal

carcinoma can rarely be cured.[10] Therefore, it is questionable whether patients who are treated for these advanced tumors should receive the same thorough follow-up schedule as patients with less advanced primary tumors.

In the period after the detection of cancer recurrence in patients after total laryngectomy, life was characterized by considerable disease-specific morbidity. These patients spent a lot of time at the hospital for treatment and interventions. Many of them lost the ability to speak, and 10% needed psychiatric help. Before interventions are carried out for the purpose of tumor detection, it should be verified whether treatment options are available if the patient is found to have cancer recurrence.[11] The value of performing interventions with the aim of detecting cancer should be discussed with the patient to avoid spending a lot of scarce time left at the hospital.

Thus, we can conclude that despite the frequent and long-term follow-up program, only four patients of the 259 potentially benefited from this program. Only one of these recurrences was detected in an asymptomatic stage. Because more than 90% of the cancer recurrences were detected within 2 years after total laryngectomy, we would propose a short-term follow-up program of 2 years after laryngectomy that focuses on possible treatment options in case of cancer recurrence, the comorbidity of the patient, and is based on care instead of cure.

Conclusion

In the past decades, the prognosis of laryngeal cancer has improved only slightly. The main aim of conducting a follow-up program for patients with laryngeal carcinoma after total laryngectomy should not be the detection of asymptomatic cancer but should emphasize on care instead of on presymptomatic cancer recurrence detection. This applies especially to patients who have already received radiotherapy. Perhaps a specially trained nurse could assume the task of offering guidance and supportive care to these patients in a shortened follow-up program. This study did not include the other motives for applying an intensive follow-up program.

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Part III

Changing the follow-up program

Chapter 5

Screening for local and regional cancer recurrence in patients curatively treated for laryngeal cancer: definition of a high-risk group and estimation of the lead time

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Abstract

Background.
All patients treated for laryngeal cancer are offered the same follow-up schedule to detect asymptomatic locoregional recurrences. In this study, we evaluated the prognostic profile of patients for cancer recurrence and estimated the lead time.

Methods.
A cohort study was performed between 1990 and1995. Cox proportional hazards model was used to analyze the prognostic factors. The effect of altering the follow-up for asymptomatic recurrence detection was determined after estimating the lead time.

Results.
The variables cT classification, smoking, and histological grade proved to be prognostic factors. The risk of locoregional failure was 15% in the low-risk group versus 29% in the high-risk group. The estimated lead time was 2 to 4 weeks.

Conclusion.
Risk profiles for locoregional relapse were defined. Intensifying the follow-up schedule is not advisable because the lead time is very short. An excessively high number of routine visits would have to be performed to increase the detection rate for asymptomatic recurrences.

Introduction

In the Netherlands, as throughout Western Europe, the most common location of head and neck cancer is the larynx.[1] After curative treatment for laryngeal cancer, patients enter a uniform, nationwide follow-up program. They are put on 1 of 2 schedules: a minimum of 17 routine visits at fixed intervals and declining frequencies over a period of 5 years; or 22 routine visits over a period of 10 years.[2] The main aim is to detect local or regional cancer recurrence while it is still asymptomatic.[3,4] This follow-up program was designed on the basis of extensive clinical experience and national consensus. All curatively treated patients are enrolled in this follow-up program. Some of them, as it turns out, run a higher risk of locoregional cancer recurrence than others.[5,6]

Previous studies on follow-up in head and neck cancer conclude that patients with upper-airway malignancies run a high risk of developing local or regional cancer recurrence and second primary malignancies.[7] In the literature, the locoregional recurrence rate of laryngeal cancer is usually given within the broader context of recurrent head and neck cancer and is mostly used to evaluate a new treatment protocol for a specific tumor stage. Reported recurrence rates range from 16% to 32%, while some studies on advanced primary tumors report rates up to 50%.[8,9] The most frequent sites of locoregional cancer recurrence are the larynx or neopharynx, including stomal recurrences, followed by the regional lymph nodes.[10] Grau et al. found that the duration of follow-up could be shortened because most relapse-related deaths occurred within the first 3 years.[11] However, they did not analyze to what extent asymptomatic recurrence detection is preferable to symptomatic detection in terms of potential survival benefit or cancer mortality reduction.

Several studies concentrated on prognostic factors for local or regional cancer relapse in patients with laryngeal or other head and neck cancers. Although calculations were performed to identify prognostic factors, it was not clear whether these high-risk patients would benefit from intensified screening.[5,6,12]

The present study investigated whether it is possible, during the follow-up of curatively treated laryngeal cancer patients, to recognize the clinical risk factors of local or regional cancer recurrence. We defined a low-risk and a high-risk group for locoregional cancer recurrence in an effort to personalize the current follow-up program and perhaps to limit participation in it to high-risk patients. In this paper, we discuss the effect of the follow-up program on therapeutic options, cancer-specific mortality, and survival of patients with asymptomatic locoregional cancer recurrence. The actual asymptomatic recurrence detection rates were used to

estimate the lead time (the interval at which a tumor is detected prior to the presentation of symptoms). The estimated lead time was then used to evaluate how intensifying the follow-up schedule would affect the detection rate for asymptomatic recurrences.

Patients and methods

A cohort study was performed on all the consecutive patients with laryngeal cancer who were referred to our clinic between January 1990 and January 1995. The following inclusion criteria had to be met: primary tumor of the larynx; histologically proven squamous cell carcinoma; and initial treatment with curative intent.

After treatment, all the patients entered the follow-up program. It comprised a routine visit every 2 months in the first year of follow-up, every 3 months in the second year, and every 4 months in the third year. In the fourth and fifth years, the patient was seen every 6 months. Some patients were screened annually for up to 10 years. Patients were free to make additional appointments if they had complaints or questions. An interview was held at each routine visit or at each extra visit between the prescheduled visits. Furthermore, a complete physical examination was performed on the head and neck, including palpation of the neck region, pharyngoscopy, and laryngoscopy. The otorhinolaryngologist and the radiation oncologist conducted these examinations alternately.

Data were retrieved from the patient's medical records at the departments of Otorhinolaryngology and Radiotherapy. Any precise complaints that indicated tumor recurrence and/or physical evidence of tumor recurrence were recorded at each visit.

Data Analysis

Data on patient, tumor, and treatment characteristics were collected and stored in a Microsoft Access database designed for the study. Recurrence and survival curves were computed by the Kaplan-Meier method. Differences between patient and tumor variables were tested with the chi-square test, using SPSS version 12.0.1. The uni- and multivariate analyses were performed with the statistical software SAS version 8.2.

Patients with locoregional recurrences were divided into 3 groups: patients with screen-detected asymptomatic locoregional recurrences; patients with symptomatic recurrences detected at a prescheduled visit; and patients with a sympto-

matic recurrence that was detected at an additional visit. These groups were compared in terms of the therapeutic options applied to the recurrence and the effects on cancer-specific mortality and survival. Time to recurrence was calculated using the date of histologic proof of the primary tumor and of the cancer recurrence.

A number of patient and tumor characteristics that were thought to have prognostic influence on local or regional cancer relapse were analyzed: age (dichotomized into ≥ 65 years vs < 65 years); sex; smoking after primary laryngeal tumor detection (continuation vs cessation); daily alcohol consumption (> 6 units a day vs none or ≤ 6); tumor stage (II–IV vs I); histological differentiation (poor vs well/moderate); cT classification (T2–4 vs T1); cN classification (N+ vs N0); localization (supraglottic vs glottic); and therapy applied to the primary malignancy (radiotherapy alone vs surgery alone, or surgery combined with radiotherapy). Risk factors were determined at the baseline of the initial treatment of cancer except for smoking.

First, the impact of assumed prognostic factors on disease recurrence was studied univariately, together with the 95% confidence interval and p value, by applying the Cox proportional hazards method. All prognostic factors with a p value ≤ 0.1 were analyzed multivariately. The multivariate analysis with a stepwise backward technique was used, including the possible factor combinations, to assess independence of the prognostic factors. The independent risk factors calculated with this technique were used to construct 8 different prognostic profiles. Their rates over time were calculated for each of these profiles.

Next, it was attempted to estimate the lead time, meaning the length of time by which the detection of the locoregional cancer recurrence had been brought forward by the current follow-up schedule. We used the formulas developed to estimate the lead time in the general screening program for breast cancer, which have been described by Straatman et al.[13] and Van Gils et al.[14]. These formulas show that lead time can be described based on the observed prevalence of recurrence detected at a screening examination and on the occurrence of recurrences during intervals between surveillance examinations taking place at times $t_1, t_2, \ldots, t_n$.

The probability that cancer will be detected at screening *"j"* is given by $P[S_j] \approx r/\lambda [1- e^{-\lambda\Delta t}]$. Detection of a recurrence in the interval between 2 scheduled visits is given by $P[I_j] \approx r\Delta t - r/\lambda [1 - e^{-\lambda\Delta t}]$. Here *r*, locoregional cancer incidence; $1/\lambda$, mean sojourn time; meaning the time in which preclinical cancers are detectable before becoming clinically manifest. And Δt, length of the screening interval in years. Actual data of asymptomatic and symptomatic cancer recurrence detection

in our study group were used to calculate the mean lead time. With the above mentioned formulas at hand we then evaluated how altering the number of routine visits during follow- up affected the detection rates for asymptomatic recurrence.

Results

Population

A total of 402 patients with laryngeal cancer met the inclusion criteria. Most of the patients (62.7%) had glottic laryngeal cancer, many (37.1%) had supraglottic laryngeal cancer, and a single patient (0.2%) had subglottic laryngeal cancer. The peak incidence was in the seventh decade of life and the man-to-woman ratio was 8.6:1.0. The mean duration of follow-up was 61 months, with a median of 66 months. The 5-year overall survival rate for the 402 patients was 73%.

Survival

Overall survival calculated from the detection date of the recurrence (date of positive histology) in the 94 patients who had a relapse was 69% at 12 months and 47% at 5 years (Figure 1).

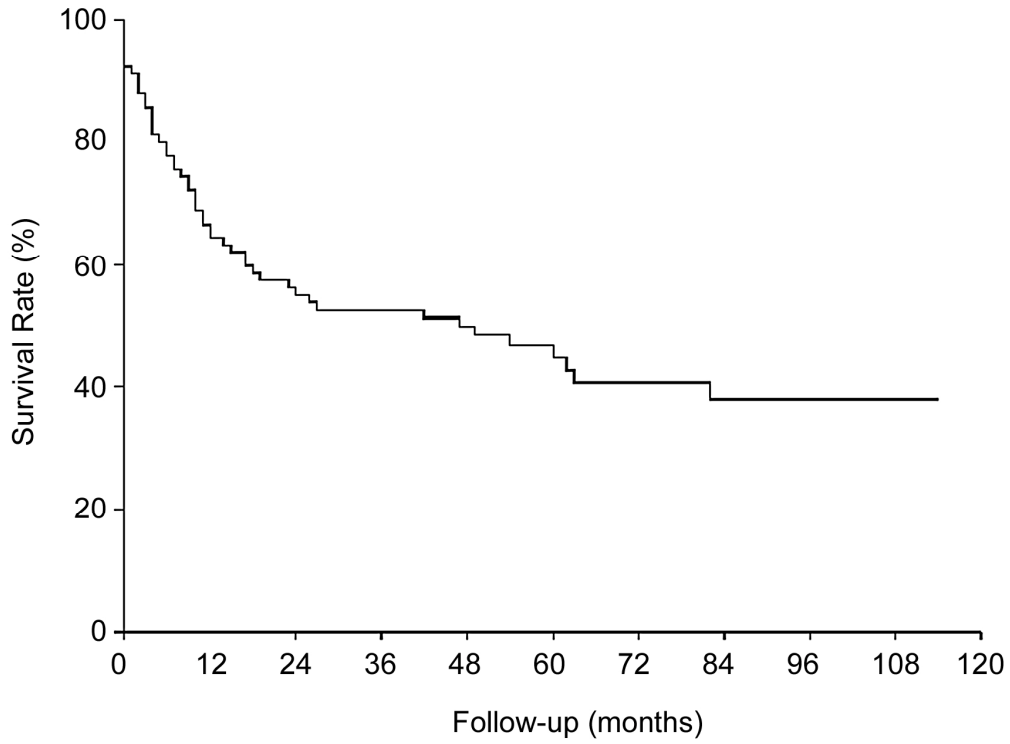

Figure 1. Overall survival from detection date of locoregional recurrence.

Follow-up protocol

According to the medical records, the 402 patients made 4639 routine visits to our clinic. Thus, 98% of the planned routine visits took place.[15]

Local and regional cancer recurrence

A total of 94 (23%) of the 402 patients had a local and/or regional cancer relapse. In 70 patients (74%), it developed at the primary tumor site, whereas 10 of them also had a regional recurrence in the neck. In 24 patients (26%), cancer recurrence was detected at a lymph node in the neck, without any local relapse.

In the majority of the 70 patients with a local recurrence, the therapy applied was with curative intent (60 of 70, or 86%). By the end of the follow-up period, 33 of the patients who were diagnosed with local cancer recurrence had died (47%); 27 of these 33 (82%) deaths were due to cancer.

In the group of patients with recurrence in the neck (*n* = 24), 14 of the 24 (58%) patients were treated with the intent to cure. During the follow-up, 17 of the 24 patients died (71%), 13 of them due to cancer (76%). In the 10-year follow-up program, 88% of the local and regional recurrences developed in the first 3 years. The mean interval was 19 months; the median was 12 months (Figure 2).

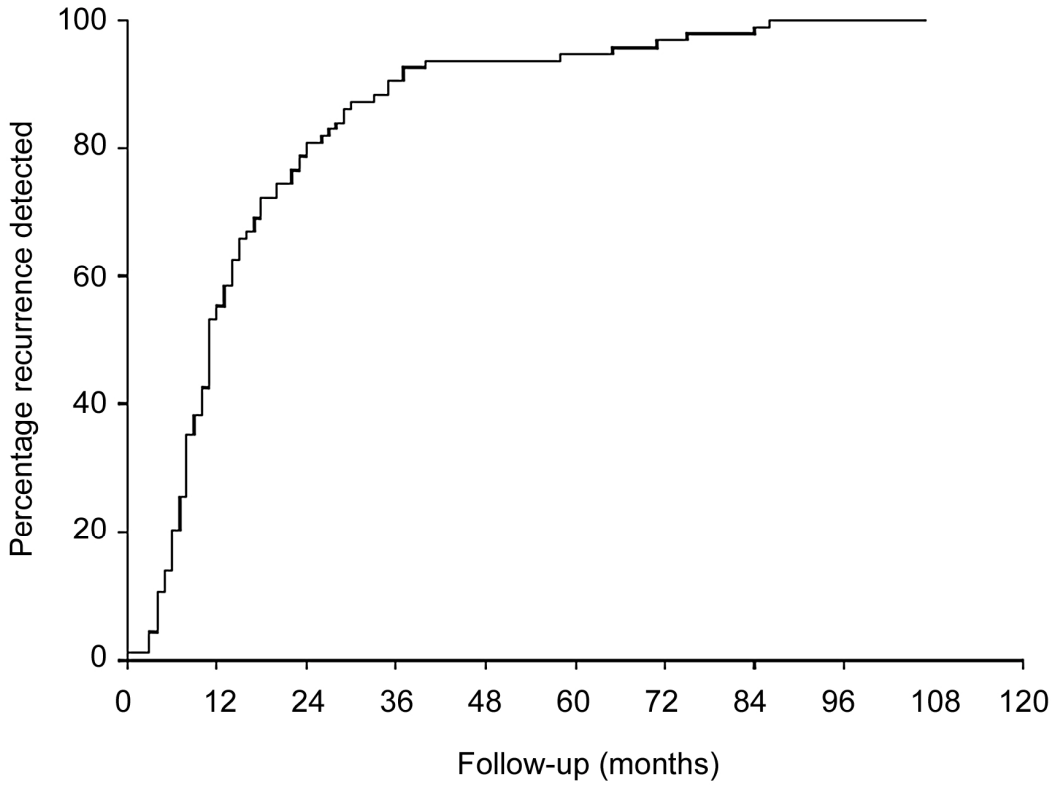

Figure 2. Interval between diagnosis of the primary laryngeal carcinoma and diagnosis of the locoregional recurrence.

Asymptomatic locoregional recurrence detection and treatment options, survival, and mortality

Eighty five of the 94 patients could be assigned to 1 of 3 groups. The first consisted of patients with screen-detected locoregional recurrences (*n* = 19). The second consisted of patients with a locoregional recurrence detected at a routine visit while symptoms were present (*n* = 41). And the last group comprised those patients whose tumor had been detected at an additional visit, which was arranged because symptoms had emerged (*n* = 25). In 9 patients, the mode of detection was either unknown or the recurrence was detected at an extra visit without symptoms present. There was no difference between the 3 groups with respect to the time interval between the primary malignancy and the recurrent tumor (*P* = 0.71). The groups were comparable for age, sex, tumor stage, cT classification, cN classification, histology, and therapy (surgery, radiotherapy, or a combination) for the primary tumor.

Furthermore, no difference was found between the types of therapy applied (surgery and/or radiotherapy) for the locoregional recurrence. Also no difference was found in the intention of the therapy applied, be it curative or palliative. The cause of death—from cancer or due to other reasons— did not differ among the 3 groups. Finally, no difference was found among the groups with respect to survival.[15] Table 1 summarizes the number of T1 patients and the *P* values.

Table 1. Therapy intention, treatment modality, cause of death, and survival by mode of recurrence detection (*n* = 85).

	Screen-detected (*n* = 19)	Symptomatic/ routine visit (*n* = 41)	Symptomatic/ extra visit (*n* = 25)	*p*-value
Therapy intention				0.19
Curative	14	36	17	
Palliative/No therapy	4	5	7	
Unknown	1	0	1	
Treatment modality				0.84
Surgery	12	33	16	
Radiotherapy	1	2	2	
Combined	1	2	0	
Unknown	5	4	7	
Cause of death				1.00
Cancer	8	19	10	
Other	1	3	2	
Unknown	10	19	13	
5-year survival	45%	53%	54%	0.89

Risk of local or regional cancer relapse

In the univariate analysis, the cT classification, smoking habit, cN classification, localization of the primary malignancy, tumor stage, and histology were found to influence the risk of local or regional cancer relapse. These variables were then analyzed multivariately and were computed again in the patient group to establish their multivariate *P* values. Primary tumor cT classification (*P* = .004), continuing to smoke after detection of the primary malignancy (*P* = .09), and poor histological differentiation (*P* = .001) proved to be independent prognostic factors (Table 2).

Table 2. Hazard ratio of prognostic factors for locoregional recurrence.

Prognostic factor	Number	Assumed high risk	Hazard ratio	95% CI	*p*-value (univariate)	*p*-value (multivariate)
Gender	360	Male	0.83	0.45-1.53	0.55	
Alcohol	53	≥ 6 units	1.35	0.76-2.39	0.30	
Age (years)	184	≥65	0.98	0.65-1.48	0.92	
Therapy primary tumor	326	Radiotherapy	1.26	0.71-2.22	0.43	
cT classification*	245	T_{2-4}	2.19	1.39-3.47	0.0008	0.004
Smoking*	86	Continuation	1.46	0.93-2.29	0.10	0.09
cN classification	61	N+	1.61	0.95-2.73	0.08	
Localization	149	Supraglottic	1.78	1.19-2.67	0.005	
Tumor stage	248	II-IV	2.14	1.35-3.38	0.001	
Histology (differentiation)*	64	Poor	2.34	1.49-3.68	0.0002	0.001

*Independent prognostic factor by multivariate analysis.

The largest difference in the risk of locoregional cancer relapse was found by applying the dichotomization cT 1 versus cT 2–4. By stratifying the study population according to the 3 prognostic factors mentioned above, 8 goups (I–VIII) could be formed. We calculated the risk that locoregional cancer recurrence would develop in these groups. Table 3 shows the proportion of patients with loco-regional cancer relapse during the follow-up period.

Table 3. Risk of locoregional recurrence during follow-up in relation to combinations of prognostic factors.

				Risk by month								
Histology	cT Classification	Smoking	Group	12	24	36	48	60	72	84	96	108
Well/moderately differentiated	1	Cessation	I	0.06	0.10	0.12	0.12	0.13	0.13	0.15	0.16	0.18
		Continuation	II	0.09	0.14	0.17	0.18	0.19	0.20	0.21	0.22	0.25
	2-4	Cessation	III	0.12	0.19	0.22	0.24	0.24	0.25	0.27	0.28	0.32
		Continuation	IV	0.17	0.27	0.31	0.33	0.34	0.35	0.38	0.39	0.43
Poorly differentiated	1	Cessation	V	0.13	0.20	0.24	0.26	0.26	0.27	0.29	0.30	0.34
		Continuation	VI	0.18	0.28	0.33	0.35	0.36	0.37	0.40	0.42	0.46
	2-4	Cessation	VII	0.23	0.36	0.42	0.44	0.45	0.47	0.49	0.51	0.56
		Continuation	VIII	0.33	0.48	0.55	0.58	0.58	0.60	0.63	0.65	0.70

A risk of 20% or less was considered a relatively low risk for locoregional cancer recurrence. Therefore group I (*n* = 114) formed the low-risk group, whereas groups II to VIII (*n* = 288) were combined to form the high-risk group. This way there would still be a sufficient number of patients in the low-risk group. Moreover, there would be a big difference in risk between the low- and high risk groups according to Table 3. The same calculation was performed on these 2 groups as on groups I to VIII. The low-risk group had a locoregional failure risk of 15% compared to 29% in the high-risk group over a period of 5 years. There was a significant difference in risk of locoregional recurrence among these groups (*P* = .004). The overall risk of locoregional failure in all the patients (*n* = 402) over a period of 5 years was 25% (Figure 3).

Estimating the lead time

The length of time by which the detection date was brought forward prior to presentation of symptoms was estimated using the current mode of follow-up examinations (history and physical examination). It was difficult to enter the data derived from our population into the lead-time formula because not all the patients had adhered precisely to the schedule of routine visits. Also, the interval between the routine visits differed each year. To simplify our calculation, the duration of follow-up was limited to 3 years and the interval between the routine visits was set at 3 months on average, meaning that 12 routine visits were conducted. In our patients with laryngeal cancer who were treated with curative intent, the 3-year locoregional relapse rate was ~25% (Figure 3).

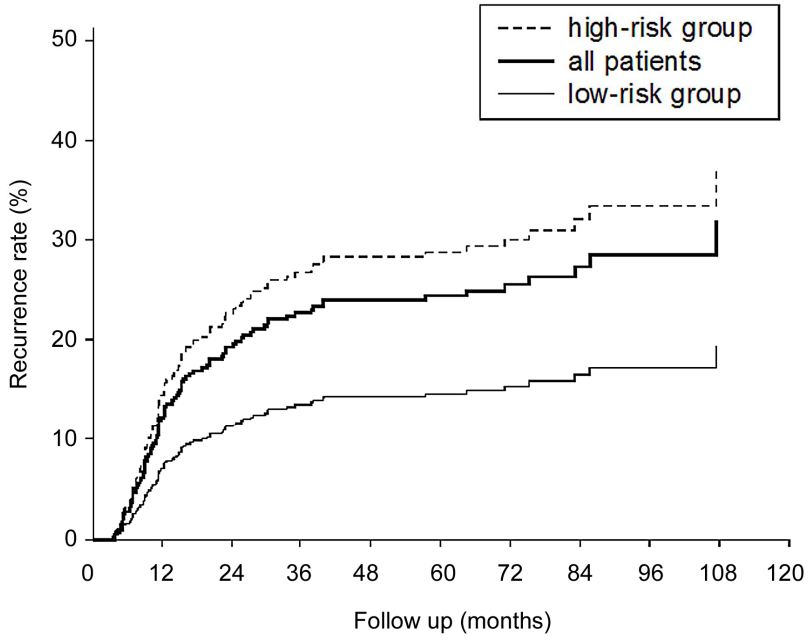

Figure 3. Locoregional recurrence rate for low- and high-risk group.

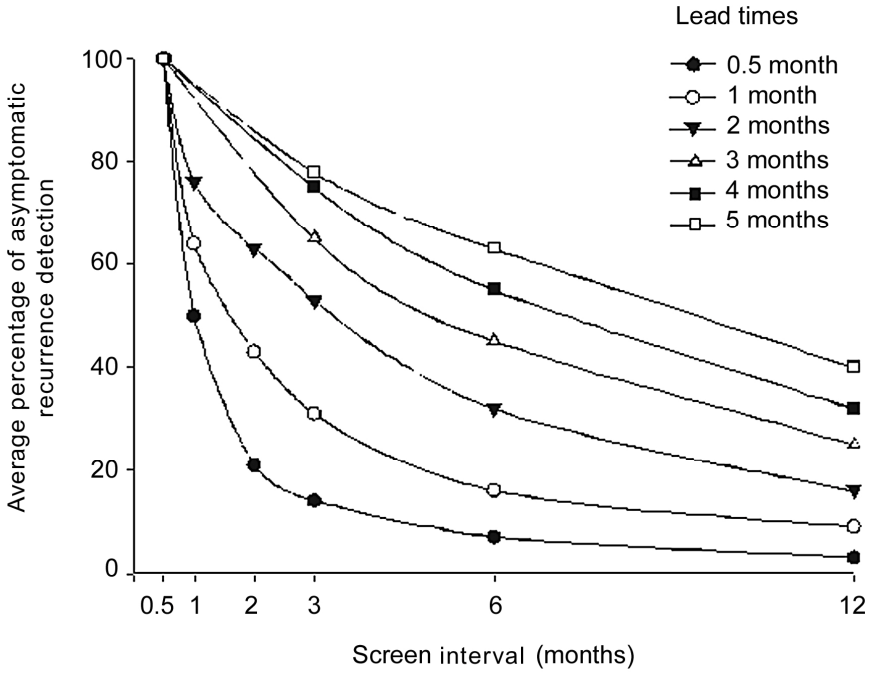

Figure 4. Detection rate of asymptomatic locoregional recurrences by variation in screening interval and lead time.

Figure 4 shows the predicted asymptomatic screen-detection rates using the formula previously derived, with various lead times of 0.5 to 5 months and screening intervals ranging from half a month to 12 months. With a lead time of 2 months (third line from below) and a visit interval of 3 months, the average percentage of asymptomatic tumors detected at each routine visit would be 53%. Monthly intervals (instead of tri-monthly) would increase the detection rate to 76% (same line shifts to the left). With intervals every 6 or 12 months, the detection rates would be 32% and 16%, respectively (same line shifts to the right). In our population, the asymptomatic screen-detection rate turned out to be 20%. According to Figure 4, the lead time must be ~2 to 4 weeks (a point between the lowest line and the second lowest line in the figure).

If the screening interval is set at 1 month and the lead time is set at 0.5 month, according to Figure 4, 50% of the recurrences will be detected asymptomatically. In order to estimate a kind of “number needed to screen" to detect one case of asymptomatic recurrence we made a very rough calculation comprising a cohort of 400 patients developing 100 recurrences within 3 years. In a cohort of 400 patients under surveillance for 36 (months) ≈ 14,000 routine visits will achieve 50 screen-detected tumors. A lead time of 1 month would detect ~64 asymptomatic recurrences (Figure 4). Therefore, to screen-detect 1 locoregional cancer recurrence, 14,000/50 = 280 or 14,000/64 = 219 routine visits would have to be conducted.

Discussion

Almost one-quarter of the patients who received curative treatment for laryngeal carcinoma at our center were diagnosed with local or regional cancer recurrence. They had all entered the same strict nationwide follow-up program that was set up to detect asymptomatic local and regional cancer recurrences. Despite the fact that there are only limited therapeutic options left for some patients who had undergone total laryngectomy for advanced-stage disease.[16]

Asymptomatic locoregional cancer detection did not lead to differences in the therapy applied, to reductions in cancer-specific mortality, or to improved survival. In addition, the detection date of locoregional cancer recurrence was not found to have been brought forward by the screening program. This suggests that a short lead time should be taken into consideration in screening programs for recurrence in patients treated for laryngeal cancer.

The follow-up program runs for 10 years after treatment for the primary laryngeal tumor. The locoregional recurrences mainly developed in the first 3 years. Thus, the question arises as to whether the follow-up program can be shortened to 3 years. This would not disregard the interests of patients who develop metastases, because most of the distant metastases develop in the same period.[17] Second primary malignancies in the head and neck region develop at a constant rate over the follow-up period, but their incidence is low compared to locoregional cancer recurrences.[18]

To determine which patients run a high risk of local or regional cancer recurrence, we analyzed a set of variables to evaluate their prognostic value. Three independent variables were found, and calculations on recurrence rates were performed on combinations of these variables. Localization supraglottic, tumor stage II to IV, and N+ classification seem to be risk factors in the univariate analysis. In the multivariate analysis, however, they proved to be interdependent. Compared to glottic tumors, supraglottic tumors are more often detected at a more advanced stage, including the cT classification. Ultimately, a low-risk group and a high-risk group were formed. The risk of local or regional cancer recurrence in the low-risk group was 15% compared to 29% in the high-risk group during the first 5 years of follow-up. In our opinion, the difference in recurrence risk between the low- and high-risk groups was not large enough to justify restricting participation in the follow-up program to the high-risk group.

The value of the screening program would improve if all the locoregional recurrences were detected at an asymptomatic stage. This could be accomplished by intensifying testing, ie, arranging more frequent routine visits or by developing

more sensitive techniques to detect asymptomatic recurrence. As the majority of patients were no longer asymptomatic when the locoregional recurrence was detected, and the average frequency of routine visits was once every 3 months over the first 3 years of follow-up, it can be expected that only a short time is spent in a detectable preclinical phase (the sojourn time).[19] A short sojourn time implies that to detect the lesion earlier, routine follow-up visits should be planned at short intervals. Our estimates point to a lead time of at most 4 weeks.

This very short lead time explains the large number of recurrences that were detected at a routine visit when symptoms were already present. Patients whose symptoms emerged just after a routine visit might not have paid them much attention because of the recent reassurance. It was also possible that some patients waited with their symptoms until the next prescheduled visit. A rough estimate showed that the aim of enhancing the rate of asymptomatically detected locoregional recurrences would require an excessive number of prescheduled visits.

Conclusion

Despite the great efforts made by patients and physicians to adhere strictly to the follow-up schedule, there are no indications that asymptomatic locoregional recurrence detection results in better treatment options, reduced cancer mortality, or improved survival. Important prognostic factors for local or regional cancer recurrence appeared to be continuation of smoking after treatment, the cT classification of the initial tumor, and the histology. It was possible to define a high-risk group for locoregional cancer recurrence, but the difference in risk between the low-risk and the high-risk groups was not substantial. The percentage of recurrences in the low-risk group is still high. This prevents us from withholding routine follow-up from the low-risk group without investigating how so doing would affect their life expectancy.

To detect more recurrences at an asymptomatic stage, an enormous number of pre-scheduled visits would have to be added to the follow-up program, due to the (estimated) short lead time. For now, the emphasis of the follow-up program should be on the emotional well-being of the patient and on the treatment of complications of the therapy applied. Patients should be strongly encouraged to refrain from smoking. After the third year of follow-up, the screening program can be discontinued.

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Chapter 6

Effect of routine follow-up after treatment for laryngeal cancer on life expectancy and mortality: results of a Markov model analysis

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Abstract

Background.
Routine follow-up is offered to all patients with laryngeal cancer who are treated with curative intent. Although time and resources are devoted to surveillance, the effect of asymptomatic recurrence detection is not well understood. For this study, the authors evaluated the effect that routine follow-up may have on life expectancy and disease-specific mortality rate for patients with laryngeal cancer.

Methods.
Using a Markov model, a cohort simulation was performed on 4 hypothetical age groups of patients with laryngeal cancer. Three different follow-up strategies were compared -the current schedule, no follow-up, and the perfect follow-up- in which all recurrences were detected asymptomatically. Sensitivity analyses were performed to study the impact of variations in the transition rates on life expectancy.

Results.
Compared with no follow-up, the current schedule showed a gain in life expectancy with a range from 0.3 – 1.5 years that decreased with advancing age. Abolishing the current follow-up schedule raised the disease-specific mortality rate; the increase ranged from 2.8% to 5.9%. Variations of +/- 25% in the transitions rates produced only a modest effect on life expectancy.

Conclusions.
A small reduction in life expectancy was observed when follow-up was withheld from the majority of patients. Disease-specific mortality rates rose when no follow-up was provided. These rates probably were overestimated. A simplified version of the current follow-up protocol may be implemented.

Introduction

Posttreatment surveillance is part of the treatment protocol for patients with laryngeal cancer, because its believed that the detection of asymptomatic recurrences or second primary tumors is an important factor in prolonging life expectancy (LE). Follow-up also is intended to reduce disease-specific mortality (DSM). The other objectives of follow-up – detection and treatment of complications, evaluation of medical treatment, and provision of psychosocial support – were not considered in the current study.
Several studies have been published on the value of follow-up for patients with head and neck cancer. Some authors advocate thorough follow-up, citing a substantial incidence of recurrences and second primary malignancies. Others recommend limiting surveillance to the first years after curative treatment.[1-3] Unfortunately, this debate is hampered by a lack of comparative empirical data. Postoncologic surveillance has been evaluated for several other malignancies; however, no benefit has been observed for patients with breast cancer or colon carcinoma.[4-7] This lack of benefit may be caused by the differences between post-oncologic surveillance programs and nationwide primary cancer screening programs. Patients who already have received oncologic treatment but go into recurrence, have a poorer prognosis compared with patients who have primary malignancies. Some other factors probably also are involved: the limited therapeutic options in the event of cancer recurrence and, applicable to both the post-oncologic surveillance and the general screening programs: the detection of slow-growing tumors (length-time bias) and the magnitude and adjustment of the lead-time.[8-11]

According to the current protocol, patients who have received curative treatment for laryngeal cancer, continue to visit our clinic regularly, 22 times over a period of 10 years. Surveillance is more intensive during the first years after treatment. One objective is to detect recurrences, because the rate of recurrence is higher early during follow-up. Another objective is to treat any posttreatment complications that might arise. After they receive curative treatment, all patients enter the follow-up program, it comprises a routine visit every 2 months during the first year of follow-up, every 3 months in the second year, and every 4 months in the third year. In the 4^{th} and 5^{th} years, the patient is seen every 6 months. Many patients are screened annually for up to 10 years. Between their prescheduled visits, the patients are free to make another appointment if they notice any symptoms. Here, these visits are called extra or additional visits.[12] The follow-up schedule adopted at our clinic

conforms to the nationwide recommendations for laryngeal cancer treatment in the Netherlands.[13,14] There is no internationally accepted standard protocol.

It is not deemed ethical to conduct a randomized controlled trial in which 50% of the patients are excluded from routine follow-up without strong evidence that such surveillance is ineffective. In the current study, we evaluated the effect of the current follow-up protocol on LE and DSM. These effects were calculated and were compared with the results from 2 alternative schedules: a schedule that abolished all routine visits and another schedule that adhered to a perfectly conducted routine follow-up in which all cancer recurrences were detected asymptomatically. This exercise is performed with a Markov model, and the results were combined with data on the current follow-up of laryngeal cancer patients as observed in a previous study.[12]

Materials and methods

The study population

Measured data were derived from a cohort of 402 laryngeal cancer patients who were referred to our clinic between January 1990 and January 1995. All patients had a squamous cell carcinoma and were treated with curative intent. The most common site involved was the glottic region (62.7%) followed by the supraglottic region (37.1%) and the subglottic region (0.2%). The peak incidence was in the seventh decade of life, and the ratio of men-to-women was 8.6:1.0. The mean duration of the follow-up program was 61 months (median, 66 months). The 5-year overall survival rate for all 402 patients was 73%. During the follow-up, 156 patients developed recurrent cancer.

In 94 patients (60.2%), recurrent cancer developed at the primary tumor site or in a cervical lymph node. Fifteen patients (9.6%) developed a primary tumor in the head and neck region, and 17 patients (10,9%) developed a primary tumor in the lungs. Distant metastases were detected in 15 patients, and 15 patients developed a malignancy elsewhere in the body.

Patients with recurrent cancer were divided according to the presence of symptoms that indicated the recurrence (yes or no) and by the mode of detection (at a routine visit or at an additional visit in between the routine visits). Thirty-seven patients had a malignancy detected in the preclinical phase at a routine visit, and 101 patients had symptoms indicating recurrent cancer detected at either a routine or an additional visit.

The Markov Model

Markov models are implemented for clinical problems in which the risk of an event is continuous over time. For the current study, we used a Markov chain model that was developed previously and was intended to evaluate the effectiveness of pre-symptomatic detection of breast cancer recurrence.[15] The model allows us to make a comparison between the current protocol and various alternatives.

The progression of disease is described by the model as a finite sequence of discrete states of illness, also referred to as health states.[16] Consistent with a Markov model, we assumed that a patient is always in 1 of these health states. Transitions are possible between the various states. The model starts at a fixed stage of disease or a certain occasion within a treatment protocol. A hypothetical group of patients of the same age enters the model directly after receiving treatment for laryngeal cancer. During follow-up, the patients are cycled through this model and become redistributed in a specific time span. Because the calculations are based on proportions and rates, the absolute number of patients entered in the model is irrelevant to the outcome of the exercise.

A Markov chain model was designed to describe the history of laryngeal squamous cell carcinoma. The model recognizes 7 health states and 2 states of death (Figure 1).

At first, all patients are subsumed under the health state ‘curative treatment for cancer’. At the end of a cycle, a fraction of the initial cohort is apportioned to subsequent states according to the transition probabilities. Patients may remain in the same state; they may develop asymptomatic or symptomatic locoregional recurrence; develop 2nd primary head and neck cancer or metastases; or they may die of some other cause. The onset of recurrent cancer is not detectable. The recurrence will be detected, either asymptomatically or in light of symptoms as the disease progresses. Subsequently, patients may recover from the recurrent cancer; or they may die of recurrent cancer or of some other unrelated cause. At the end of the simulation, all patients eventually end up in the absorbing states of ‘death from cancer’ or ‘death from other causes’. In this study, cohort simulations were performed on 4 hypothetical groups of patients aged 40, 50, 60, or 70 years who were cycled through the model separately. The duration of each cycle was 1 year.

Transition rates

Transition rates are defined as the proportion of patients who shift from 1 state to another during a fixed one-year interval. These rates are depicted in the model by

Greek letters, λ is for disease progression rate, and μ indicates the natural mortality rate.

The "i" in $\lambda_{i,j}$ refers to the transition of 1 health state to another, and "j" refers to recurrent cancer (either local or regional recurrence, metastasis or 2nd primary head and neck cancer). The rates presented here were derived from a study by Ritoe et al., and were supplemented by findings from the literature and assumptions based on academic knowledge. [12,17] The μ (death from other causes) depends on age and sex and is considered to be equal for each health state. Mortality rates and general LE are derived from the Central Bureau of Statistics (Statistics Netherlands, 2002).[18] The explanation and calculation of the transition rates are presented in the Appendix. Table 1 lists all the transition rates used for the calculation of the 3 different follow-up strategies.

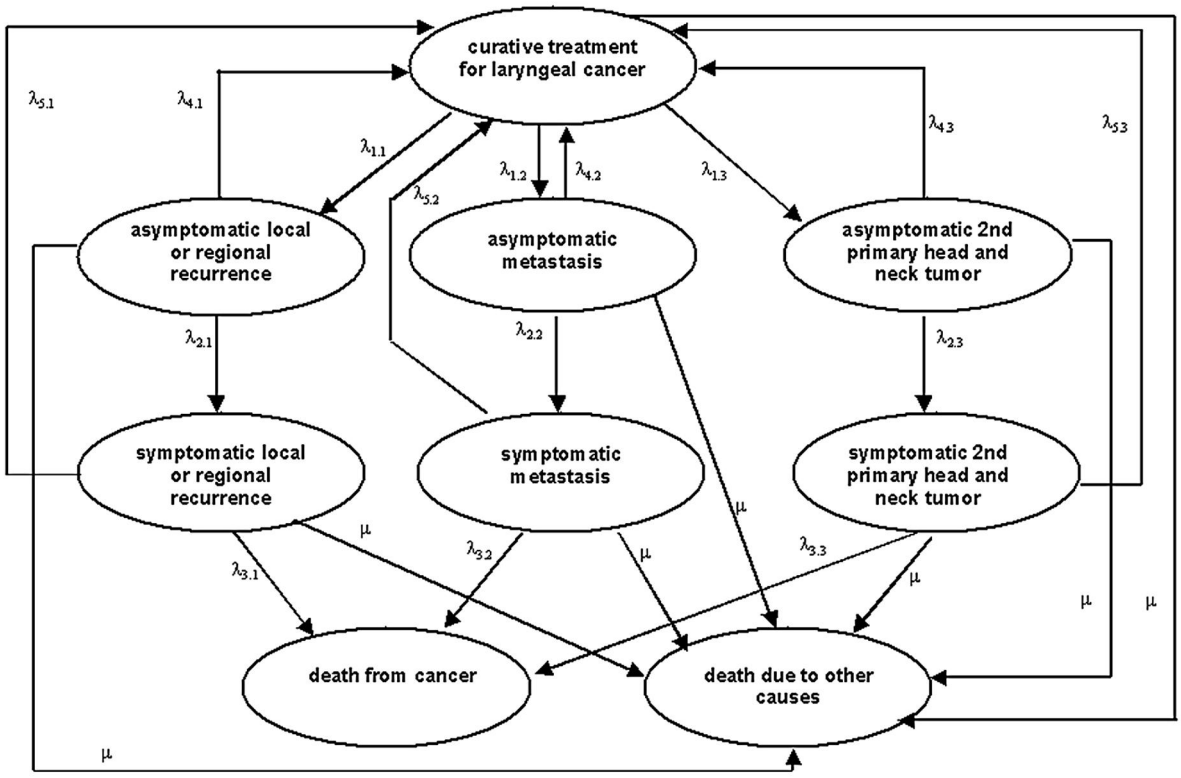

Figure 1. Markov chain model representing the history of patients who have received curative treatment for squamous cell laryngeal carcinoma

Model assumptions

Changing the current follow-up protocol does not alter the proportion of patients entering the subclinical disease state (λ_1). It is not expected that the number of

routine visits will have any influence on the mean sojourn time, i.e. the time in which preclinical cancers are detectable.

Table 1. Transition rates for the current follow-up, no follow-up, and the perfect follow-up.

Transition	Current Follow-up	No Follow-up	Perfect follow-up[a]
Curatively treated to asymptomatic state			
$\lambda_{1.1}$	0.039	0.039	0.039
$\lambda_{1.2}$	0.002	0.002	0.002
$\lambda_{1.3}$	0.114	0.114	0.114
Asymptomatic to symptomatic state			
$\lambda_{2.1}$	4.196	4.196	4.196
$\lambda_{2.2}$	3.798	3.798	3.798
$\lambda_{2.3}$	1.791	1.791	1.791
Symptomatic state to death from cancer *			
$\lambda_{3.1}$	0.107	0.109	0.106
$\lambda_{3.2}$	1.100	1.364	0.937
$\lambda_{3.3}$	0.109	0.111	0.107
Asymptomatic state to curatively treated *			
$\lambda_{4.1}$	0.165	0	0.737
$\lambda_{4.2}$	0	0	0
$\lambda_{4.3}$	0.316	0	0.923
Symptomatic state to curatively treated *			
$\lambda_{5.1}$	0.484	0.803	0.803
$\lambda_{5.2}$	0	0	0
$\lambda_{5.3}$	0.362	0.440	0.440
Any health state to death due to other causes			
μ	depending on age and gender		

* Varies by follow-up strategy
[a] All recurrences asymptomatically detected

Therefore, the transition from the asymptomatic state to the symptomatic state (λ_2) was expected to be the same for each of the follow-up strategies. Calculation of the transition rate from the symptomatic state to death from cancer (λ_3) was based on the findings in the previously conducted study. However, because survival was calculated from the date recurrent cancer was detected, we had to take into account the lead time by which the detection date was brought forward for the asymptomatic discovered malignancies. In that study the lead time for local or regional cancer recurrences was estimated to be 1 month. For metastases and 2nd primary head and neck malignancies this will be somewhat longer. In the present study it was assumed that stopping surveillance due to symptomatic recurrence detection would postpone detection by approximately 2 months. The reverse was

assumed when all recurrences were detected asymptomatically. Accordingly, during the perfect follow-up, the lead time was assumed to increase by 2 months.
Changing the current follow-up protocol influences λ_4 (the transition from an asymptomatic state to curative treatment for cancer) and λ_5 (the transition from a symptomatic state to curative treatment for cancer), because the number of patients in each state is altered. When follow-up is no longer executed, recurrences will all be detected in a symptomatic state, therefore the transition from the asymptomatic state to curatively treated state will be reduced to zero. In case of 'no follow-up', all recurrences will be detected symptomatically, resulting in different values for λ_5. In the 'perfect follow-up', all recurrences are detected asymptomatically. Because treatment is still possible in the symptomatic stage, however, λ_5 is considered to be equal to the value for 'no follow-up'. The μ (death from other causes) was considered to be the same for each health state and equal to the natural death rate of the general population and, thus, increased with age.
Patients cycled the model only once and it was assumed that patients developed only 1 type of recurrence. This can be justified by the fact that in our clinic the strict routine follow-up schedule is abandoned when patients have developed a malignancy. The recurrence rate for all types of malignancies was assumed to be equal for men and women patients.

Effect measures

Life expectancy and disease-specific mortality
In the Markov model, each patient is assigned a number of credits for the length of time spent in a specific health state. The LE is the sum of all credits obtained during the simulation and is determined by the route of states that each patient has taken. The outcome of LE for the current protocol was calculated for the separate age groups and was compared with 2 other situations: no follow-up and the perfect follow-up, in which all cancer recurrences are detected asymptomatically. Using the Markov model, the DSM rates were calculated.

Sensitivity Analysis
Estimates of the value of transition rates contain a certain amount of uncertainty. A sensitivity analysis was performed to investigate the impact of variations in the transition rates on the results. All transition rates were varied by + or - 25% of their value. They were varied grouped together, i.e. λ_1 was varied for all types of malignancies together ($\lambda_{1.1}$, $\lambda_{1.2}$, $\lambda_{1.3}$). The impact on the absolute length of LE and

the gain in life years was determined for men aged 40 years, because it was expected that variations would have the greatest impact in this age group. The impact was then compared to their LE in the current follow-up protocol (27.8 years). First, all transition rates were varied individually, and the results were displayed. Additionally, we investigated the effects of a model that included the most positive and most negative assumptions for all parameters in 1 model.
The Markov model was constructed with the software Tree Age DATA 4.0. Statistical Software (SAS version 8.2) was used to calculate the parameters, LE, DSM and to perform the sensitivity analysis.

Results

Life expectancy and mortality

The difference between the current follow-up strategy and no follow-up with respect to LE showed a decrease that ranged from 1.2 – 0.8 years for men aged 40 years and 50 years and a decrease of 0.4 years - 0.3 years for men aged 60 years and 70 years. In women, the impact of discontinuing follow-up had a slightly greater impact on reducing LE. The increase in the DSM rate seems high in the group of patients aged 40 years (5.6% for men and 5.9% for women). This percentage quickly reduces to 2.8% and 3.3% for men and women aged 70 years. When the perfect follow-up schedule is conducted, the estimated increase in LE in men aged 60 and 70 years will be 1.3 and 0.5 years, respectively. Results are summarized in Table 2.

Table 2. Effect of three follow-up strategies on life expectancy and cancer-related death in patients aged 40, 50, 60, and 70 years.

Follow-up schedule	Life expectancy (in years) men and [women]			
	Age 40	Age 50	Age 60	Age 70
Current follow-up	27.8* [30.2]	22.2 [24.9]	16.2 [19.2]	10.5 [13.1]
No follow-up	26.6 [28.7]	21.4 [23.9]	15.8 [18.5]	10.2 [12.8]
Perfect follow-up [a]	31.9 [35.0]	24.7 [28.0]	17.5 [20.9]	11.0 [13.9]
Life expectancy (in general population)	*37.0 [41.2]*	*27.7 [31.9]*	*19.1 [23.1]*	*11.8 [14.9]*
	Cancer-specific mortality (in%) men and [women]			
Current follow-up	42.7 [46.4]	33.6 [37.9]	23.9 [28.6]	14.7 [18.9]
No follow-up	48.3 [52.3]	38.5 [43.2]	27.9 [33.1]	17.5 [22.2]
Perfect follow-up [a]	24.3 [26.9]	18.4 [21.2]	12.6 [15.3]	7.3 [9.6]

[a] All recurrences are asymptomatically detected at a routine visit
* Base value for sensitivity analysis

Sensitivity analysis

In the sensitivity analysis, the most important parameter determining LE turned out to be variations in $\lambda_{1.}$ When the number of patients who developed an asymptomatic cancer recurrence was raised by 25% the LE declined by 1.2 years. Decreasing the asymptomatic recurrence rate resulted in an increased LE of 1.6 years. However, this transition rate is not influenced by the follow-up program. The variation in λ_3 also influenced LE. The percentage of patients who die after developing recurrent cancer, however, will be influenced particularly by their remaining therapeutic options after recurrence. The influence of changes in the other transitions rates only lead to small changes in the LE. Table 3 lists all of the variations in transition rates and their calculated LE ranges. Table 4 lists the boundaries within which LE can differ, from most positive to most negative, in the sensitivity analysis for all $\lambda_{i.j.}$ ranges.

Table 3. Sensitivity analysis: range +/- 25% for all lambda values in men aged 40 years with a life expectancy of 27.8 years.

Transition	Basis Value	-25%	Life expectancy	Life years gained [a]	+25%	Life expectancy	Life years gained [a]
Curatively treated to asymptomatic state $\lambda_{1.1}$ $\lambda_{1.2}$ $\lambda_{1.3}$	0.039 0.002 0.114	0.029 0.002 0.086	29.4	+ 1.6	0.049 0.002 0.142	26.6	- 1.2
Asymptomatic to Symptomatic state $\lambda_{2.1}$ $\lambda_{2.2}$ $\lambda_{2.3}$	4.196 3.798 1.791	3.146 2.848 1.341	27.8	0	5.246 4.748 2.241	27.8	0
Symptomatic state to death from cancer $\lambda_{3.1}$ $\lambda_{3.2}$ $\lambda_{3.3}$	0.107 1.100 0.109	0.080 0.825 0.082	29.4	+ 1.6	0.134 1.375 0.136	26.5	- 1.3
Asymptomatic state to curatively treated* $\lambda_{4.1}$ $\lambda_{4.2}$ $\lambda_{4.3}$	0.165 0 0.316	0.124 0.1 0.237	27.3	- 0.5	0.206 0.1 0.395	28.4	+ 0.6
Symptomatic state to Curatively treated* $\lambda_{5.1}$ $\lambda_{5.2}$ $\lambda_{5.3}$	0.484 0 0.362	0.363 0.1 0.272	26.8	- 1.0	0.605 0.1 0.452	28.6	+ 0.8

* instead of 0.0 we used 0.1 in this calculation

[a] compared to LE in the current follow-up protocol

Table 4. Sensitivity analysis for men aged 40 years: Gain in life expectancy (in years) based on the most positive and most negative set of transition rates.

	$\lambda_{i,j}$ Transition rates	
	Most positive	Most negative
Life expectancy	31.6	23.3
Gain in life years	+ 3.8	- 4.5

Discussion

As the general population ages and more women are smoking, more individuals will suffer from laryngeal cancer.[19] Accordingly, more patients will enter the follow-up program, thereby expanding the screening population. Previously, we addressed the value of the follow-up program for patients with laryngeal cancer in the Netherlands.[12] The current study, using data on follow-up in our clinic did not demonstrate any extension of survival nor any reduction in cancer-specific mortality for patients with asymptomatically detected recurrences compared with symptomatic patients.
Nonetheless, it would be unethical to withdraw patients from the current follow-up protocol without knowing how that would influence their LE and DSM. That knowledge can be produced with a Markov model that simulates the LE of patients who are treated curatively for laryngeal cancer.

The LE and DSM values were compared for 2 situations: follow-up of patients according to the existing protocol and withholding posttreatment surveillance from patients. To establish the maximal gain for these parameters, the values were also calculated for the perfect situation, in which all cancer recurrences are detected asymptomatically.
When conducting a simulation study, one objective is to describe reality in a form in which alterations of reality can be estimated. When reading the results as calculated by the model it should be kept in mind that these are not and should not be considered measured data.

When we carefully examine our results of stopping routine surveillance on LE en DSM rates, the impact seems large. This is inconsistent with the previously conducted studies on routine follow-up.[12,20,21] There are some points to be considered when evaluating the results of this study. The majority of laryngeal cancer patients are men aged $\geq$ 60 years. This group of patients accounts for 65%

of all laryngeal cancer patients in our clinic. The LE in this group is reduced only slightly when they obtain no follow-up. In younger patients and in women, the effect on LE reduction is greater. This reflects the overall longer LE in these groups in the general population. We assumed that the death from other causes is the same in the laryngeal cancer patients group as in the general population. In fact it is not very likely that this is true. There are no data however to be found in literature on this mortality rate.
Furthermore, the lead time of asymptomatic cancer detection was estimated to be 2 months. There are indications that this is an overestimate.[20] Therefore, the actual difference between the symptomatic group, and the symptomatic group may be reduced even more.

To simplify the calculations, all patients in the model only developed 1 type of malignancy. One should keep in mind that some patients go on to develop a third tumor (31%), a fourth tumor, or even more. However, this risk will not be influenced by offering routine follow-up.
Previously reported data indicate that asymptomatic patients are offered treatment with curative intent more often than symptomatic patients. However, no difference in cancer-specific mortality was observed.[12] This difference in treatment will show up when follow-up modalities are varied.
The LE and DSM values were determined for the situation in which a perfect follow-up schedule is conducted. The maximal gain in LE that could be obtained in elderly patients turned out to be disappointing.
The sensitivity analysis made it clear that the greatest variation in LE was obtained by varying 2 values: the proportion of patients entering the subclinical disease state (λ_1) and the transition rate from the symptomatic state to death by cancer (λ_3). The influence of the routine visits are either small or nonexistent. When the transition rate is varied from an asymptomatic or symptomatic state to curatively treated (λ_4 and λ_5), the differences in LE are small. The number of routine visits influences these parameters. Applying more sensitive diagnostic tests to increase the asymptomatic detection rate would be expensive. A previous study showed that the objective of more routine visits to increase asymptomatic detection is not attainable because of the high number of prescheduled visits that would be needed to increase the asymptomatic detection rate.[20]

The most serious disadvantage of using a model is that it oversimplifies the study population. Some of the implications of this are discussed above. The main problem is how to construct the model. Questions may be raised about the

assumption that patients can enter the symptomatic states only by passing through the asymptomatic states. We decided on this model because it had already been used in a study on screening for breast cancer. Yet a different model would also have been suitable in which the symptomatic and asymptomatic states are seen as separate entities. Yet it is doubtful that using such a model would have yielded a better outcome for routine follow-up. Another problem is that not all patients enter the follow-up program with the same prognosis. A previous study indicated that patients who continued to smoke after their initial treatment ran a greater risk of developing recurrent cancer compared with patients who ceased smoking. In addition, a poor histologic grade and a T2, T3 or T4 classification of the primary malignancy, will contribute to an increased risk of developing cancer.[20] Once patients have received excessive treatment for an extensive primary malignancy, fewer therapeutic options will remain in the event of recurrent cancer. Mortality rates from cancer are high – over 90% – in post-laryngectomy patients with recurrent disease. Furthermore, our model ignores the difference in cancer recurrence between patients with a limited or extensive index tumors.[21] It will be difficult, however, to include all clinical prognostic factors in the process of modeling.

Because LE in the general population is longer in women, changes in the follow-up program will have more influence on them. Because the number of women with laryngeal cancer is increasing, it is important to show the results for the female population.[19] Whether the increased LE for women compared with men applies to laryngeal cancer patients is dubious. In our previous studies, the local/ regional recurrence rate in women appeared to be the same as that in men.[12,20] However, the mode of detection in women may not be comparable. The reason is that, in the current follow-up program cancer recurrences in women usually are detected at a routine visit while symptoms are present.[12] The implications of the latter difference are not quite clear yet.

Based on the results of this study, we conclude that the current follow-up schedule has limited influence on LE in elderly patients. Follow-up should not be abolished. Rather, it should be reduced in length and intensity. The emphasis should not be on detecting asymptomatic cancer recurrence. Instead, the objective should be to provide the necessary treatment and care in case of recurrence.

Appendix: Calculation of transition rates

Calculations were performed using the cancer recurrence and survival data measured by Ritoe et al.[12]. Table 1 shows all of the transition rates for the three strategies: the current follow-up protocol, no follow-up and the perfect follow-up, when all recurrences are detected asymptomatically.

From curatively treated to the asymptomatic state: λ_1

This transition is not constant over time for locoregional recurrences or metastases. Almost 90% of all locoregional recurrences develop in the first 3 years of follow-up.[20] Metastases also are found predominantly during the first years of follow-up.[22] For locoregional recurrences and metastases, this transition can be described by an exponential declining function: $R = R_0 \cdot e^{-\lambda 1 \cdot t}$ Herein, R = number of patients recurrence free at t = 0; λ_1 = average recurrence rate per year; t = time in years. The recurrence rate declined on a S-curve. Data needed for the calculation: the proportion of patients who develop a new tumor during in 2, 3, 5 and 7 years of follow-up.

Second primary tumors develop with a constant rate in time. Our recurrence rate was consistent with findings in the literature.[17] The formula of recurrences that develop at a constant rate is given by: $\lambda = (-l/t) * \ln (R_t/R_0)$. In this equation, λ is the transition rate; R_t/R_0 = fraction of the cohort that is recurrence-free at time = t; t = time at which the recurrence-free time is measured. Data needed for this calculation: percentage of recurrence-free patients after 2, 3, 5 and 7 years of follow-up.

λ_1 was calculated for the three types of recurrences:

Locoregional recurrence	$\lambda_{1.1} = 0.039$
Metastasis	$\lambda_{1.2} = 0.002$
2nd primary tumor	$\lambda_{1.3} = 0.114$

The value of λ_1 is not altered by changing the current follow-up protocol to either ‘no follow-up’ or the ‘perfect follow-up’.

From the asymptomatic to symptomatic state: λ_2

Data on all visits to our outpatient clinic, both routine and extra visits, were collected from the patients’ medical records. Needed for this calculation: the mean sojourn time (the length of time the tumor spent in the detectable preclinical stage, ‘MST’). The time between the last visit and the visit at which an asymptomatic

tumor was detected was derived from the patient's record. The mean of these numbers defines the MST. $MST = 1/ \lambda_2$.

λ_2 was calculated for the three recurrence types:

Locoregional recurrence $\lambda_{2.1} = 4.196$

Metastasis $\lambda_{2.2} = 3.798$

2^{nd} primary tumor $\lambda_{2.3} = 1.791$

The value of λ_2 is not altered by changing the current follow-up protocol to 'no follow-up' or the 'perfect follow-up'.

From the symptomatic state to death by cancer: λ_3

The mortality rate of symptomatic patients was considered to be constant. The mathematical relation between survival and time can be described by a decreasing exponential function: $S_t = S_0 * e(-m*t)$. S_t = number of symptomatic patients with cancer recurrence at time t; S_0 = number of symptomatic patients with cancer recurrence at time 0; m= mortality rate / year (= transition rate λ_3); t = time when survival is measured. According to the DEALE method (Declining Exponential Approximation of Life Expectancy) [16], the relation between life expectancy and mortality rate is: LE = 1/m. Combining the 2 formulas results in $m = (-1/ t)*\ln(S_t / S_0)$.

Needed for this calculation is:

- the survival rate of symptomatic patients through time
- the mortality rate of patients with a specific type of recurrence

In the group of 156 patients with cancer recurrence, 73 died of cancer. Only 2 of them had a prolongation of survival beyond 5 years of follow-up. Thus, 156 – 71 = 85 patients were still alive 5 years after detection of the recurrent cancer (54.5 %).

The calculated λ_3 values were as follows:

Locoregional cancer recurrence:

94 recurrences; 39 died of cancer within 5 years. Survival: = (94-39) / 94 = 0.585

$m = \lambda_{3.1} = 0.107$ LE = 9.3 years

Metastases:

15 metastasis; 10 died of cancer within 1 year. Survival 1 year = 0.333

$m = \lambda_{3.2} = 1.100$ LE = 0.9 years

2nd primary tumor:
43 tumors; 18 died of cancer within 5 years. Survival: = 5 years = 0.581
m = $\lambda_{3.3}$ = 0.109 LE = 9.2 years
When this formula was applied a lead time of 2 months for symptomatic recurrences was assumed.

From the asymptomatic state to curatively treated: λ_4
This transition is calculated using the percentage of tumors asymptomatically detected at a routine visit. And the percentage of asymptomatic patients treated with curative intent. Using the formula : asymptomatic detection rate * cure rate gives transition rate λ_4.

Among 156 patients with cancer recurrence, the recurrences in 37 patients were detected asymptomatically at a routine visit. Of these 37 patients, 26 were treated with curative intent.

Amounts for the different types of recurrence:

Locoregional recurrence	= 19 screen detected	14 treated with curative intent
Metastasis	= 5 screen detected	0 treated with curative intent
2nd primary tumor	= 13 screen detected	12 treated with curative intent

Applying the formula, provides us with λ_4

Locoregional recurrence	$\lambda_{4.1}$ = 0.165
Metastasis	$\lambda_{4.2}$ = 0
2nd primary tumor	$\lambda_{4.3}$ = 0.316

When no routine visits take place, the detection of any cancer recurrences will be based on symptoms. Therefore λ_4 will be equal to 0 in all cases. In the perfect follow-up, all recurrences are detected asymptomatically, thereby resulting in different values for λ_4.

From the symptomatic state to curatively treated: λ_5
This transition is calculated using the formula : asymptomatic detection rate * cure rate gives transition rate λ_5.

Locoregional recurrence	= 66 detected	53 treated with curative intent
Metastasis	= 9 detected	0 treated with curative intent
2nd primary tumor	= 25 detected	11 treated with curative intent

Applying the formula provides us with λ_5

Locoregional recurrence	$\lambda_{5.1} = 0.484$
Metastasis	$\lambda_{5.2} = 0$
2nd primary tumor	$\lambda_{5.3} = 0.362$

In case of 'no follow-up', all recurrences will be detected symptomatically, resulting in different values for λ_5. In the 'perfect follow-up', all recurrences are detected asymptomatically. Because treatment is still possible in the symptomatic stage, however, λ_5 is considered to be equal to the value for 'no follow-up'.

From curatively treated, asymtomatic or symptomatic state to death by other causes: μ

Death from other causes was described in a mathematical function fitted to the data obtained from Statistics Netherlands. The following formula yielded an almost perfect fit:

μ= e (0.1202*((t + age) -106.0123) + 0.0002 * ((t + age) – 106.1023 ** 2)

μ= mortality rate per year; *age* = age at which a specific cohort of men or women started (years); *t* = time measured (years).

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Part IV

This Thesis

Chapter 7

Discussion
Summary
Samenvatting

Discussion

According to the report entitled: “Cancer in the Netherlands, trends, prognoses and implications for healthcare demands”, published by the Cancer Surveillance Committee of the Dutch Cancer Society (KWF), ageing of the Dutch population will lead to a sharp increase in the number of new patients with malignant disease in the Netherlands.[1] As a result of both this phenomenon and improved cancer survival rates, the healthcare demand will increase. Unfortunately the predicated decrease in qualified potential labor force means that the healthcare supply will actually decrease. In the report healthcare demand is subdivided into different phases, with the follow-up phase being placed between the treatment phase of the primary tumor and the treatment phase of the recurrence. Tumor-specific national guidelines usually specify the number of routine visits, the duration of follow-up and the diagnostic techniques used, yet only in the case of a few types of malignancies has the effectiveness of the employed follow-up schedule been established by means of effectiveness research.

Following curative treatment for cancer, patients’ expectations of the results of the follow-up are often very different to those of the physician. The patient mainly wants to be reassured and sometimes believes that the risk of recurrence can be reduced by carefully keeping to all routine visits.[2] The physician, on the other hand, considers the main aim of the follow-up to be screening for asymptomatic recurrence. It is assumed that detection of recurrences during an asymptomatic phase will lead to improved survival. However, follow-up has a number of other goals as well.[3,4] Providing follow-up can contribute to the patient’s wellbeing as a result of psychological support. Practice has shown, on the other hand, that pressures of work often leave little time to offer the patient support. The physician can also screen for second primary tumors and distant metastases. The incidence of second primary tumors should be sufficiently high to justify this and sufficient treatment options should be available for any distant metastases. Follow-up offers physicians a structured opportunity to record the results of the procedures and therapy they have applied and to treat complications. In practice very few of these secondary follow-up goals are achieved.[3]

In 2000 the “Laryngeal cancer guideline” was published, drawn up by the Dutch Head and Neck Tumor Working Group (NWHHT), the relevant scientific associations and the Dutch Institute for Healthcare Improvement (CBO). This guideline also included the national consensus on the frequency of routine visits

for patients treated for laryngeal cancer, as well as the duration of the follow-up schedule (minimum of 5 and maximum of 10 years) (Table 1).[4] Asymptomatic detection of local and regional recurrences is listed as the main aim of follow-up. The secondary goals are the same as those described above. Since patients with laryngeal cancer have an increased risk of a primary tumor in the lung due to their predisposing smoking behavior, lung x-rays were routinely taken until the guidelines were introduced.[5,6] At present, all treated laryngeal cancer patients are offered the same follow-up schedule, regardless of the stage of the primary tumor and regardless of which treatment options are available in the event of a recurrence.

Table 1. Follow-up schedule

	Follow-up years					
	1st	2nd	3rd	4th	5th	6th-10th
Interval between routine visits (months)	2	3	4	6	6	12
Frequency of routine visits/year	6	4	3	2	2	1
Interval between chest X-rays (months)	6	6	12	12	12	0
Chest X-ray frequency/year	2	2	1	1	1	0

In dark grey: these numbers are taken from the follow-up schedule recommended by the current guidelines.[4]

In the St Radboud University Medical Centre Nijmegen (UMCN), this follow-up schedule has been in use for decades.[7] In 2000 it was decided to subject the current follow-up schedule to a study to evaluate the effectiveness of routine visits in terms of asymptomatic detection of local and regional recurrences and second primary tumors, and to assess the effect of this asymptomatic detection on the survival rate. To this end, various cohort studies were carried out.

Results of the current follow-up program

The first study cohort comprised 402 laryngeal cancer patients.[8] Patients with recurrence during follow-up were divided into groups so that the asymptomatic patients were compared with the symptomatic patients. A second study cohort consisted of 476 patients with treated laryngeal cancer in whom the effect of screening for primary lung cancer was evaluated.[9] The third study cohort included 259 patients, 80 of whom had developed a recurrence following a total laryngectomy.[10] The remaining therapeutic options available and the ultimate

survival rate were assessed. The results of the different cohort studies resulted in this thesis.

The studies revealed that 98% of the planned routine visits in the UMCN were in fact carried out.[8] This remarkably high percentage may reflect how matter-of-course these routine visits are to the patient, as well as how important the patient considers follow-up to be.

The risk of developing a recurrence or second primary tumor during the follow-up phase was high (39%). At least 78% of all tumors and 88% of the local and/or regional recurrences were detected during the first three years of follow-up.[8,11] The chance of survival for patients with a tumor detected during the asymptomatic phase did not differ from that of symptomatic patients, nor was there any difference between the two groups in terms of the therapy provided or the risk of death due to cancer. Of those patients who had already been treated by total laryngectomy, at least 30% developed a recurrence. Only 5% of patients who developed a recurrence were still alive and disease-free at the end of the follow-up period.[10]

Just 5.2% of the patients developed primary lung cancer.[9] In nearly half the cases the lung tumor was detected during the asymptomatic stage on a routine chest X-ray. Once again, there was no difference in survival between the symptomatic and asymptomatic patient groups. Screening did, however, lead to a lead-time bias. If survival is calculated from the moment the primary lung cancer was detected, the survival time is longer for the asymptomatic patient group. This effect is due to the time of detection being earlier as the result of screening, while the actual time of death remains the same.

Risk factors play an important role in the chance of developing a recurrence, and could therefore also play a role in the drafting of a new follow-up schedule. In the above-mentioned cohort of 402 patients, we analyzed a number of anticipated risk factors in terms of developing a local or regional recurrence. A high cT classification (T2 through to T4), a poor degree of histological differentiation of squamous cell carcinoma, and continuing to smoke after treatment were all found to be independent prognostic factors for the development of a recurrence. A theoretical model found that favorable prognostic factors (T1, stopping smoking after the diagnosis of laryngeal cancer, and a moderately differentiated or well-differentiated tumor) led to a low risk of recurrence (15%), while the poor prognostic factors (T2 through to T4, continuing to smoke after treatment and a poorly differentiated tumor) led to a higher risk of recurrence (29%).[11] The

difference between the high-risk and low-risk groups is, however, not considered great enough to justify excluding the low-risk patients from follow-up.
It also became apparent that, despite the high number of routine visits, the rate of recurrences detected during the asymptomatic phase through routine visits is low (20%). The estimated lead-time for local and regional recurrence detection is 2-4 weeks with the currently employed detection methods, history-taking and full head and neck examination.[11]

Using a modeling approach with a Markov model, we attempted to estimate the anticipated reduction in life expectancy if all routine visits were halted and all recurrences were detected symptomatically. The results revealed only a slight reduction in the life expectancy (0.8-0.3 years) for men aged 50 to 70 years old.[12]

Considerations on how to improve the secondary screening programs
As stated before in the Introduction of this thesis, according to Cole and Morrison, a successful screening program requires the availability of a reasonably priced and sensitive screening test and a feasible screening schedule. In addition, the disease being screened for should have a major impact on the person affected in the future and the therapy given should be more effective in the asymptomatic stage of the disease than in the symptomatic stage. Furthermore, the number of patients in the screened group that are in the “Detectable preclinical phase” should be large enough.[13]
Are these requirements sufficiently met in the secondary screening program for laryngeal cancer?

The role of symptoms in follow-up programs
The purpose of a follow-up program is the detection of local and regional recurrences in the asymptomatic phase. In evaluating the efficacy of the follow-up program, not only the sensitivity of the “*symptoms*” is important but also the specificity. Therefore, in the group of patients who, in retrospect, had not developed a local or regional recurrence, a second primary tumor or metastases, we recorded the number of patients in whom a recurrence had unjustly been suspected. It turned out that within the group of 249 tumor-free patients, 144 (58%) had reported symptoms that could have been compatible with a local recurrence or 2nd primary tumor in the head-and-neck region. A positive lymph node had been suspected in 25 patients (10%) and a lung tumor, either metastases or a primary lung tumor, in 44 (17%). Finally, in 66 patients (26%) distant metastases had been suspected. The number of false positives was

therefore quite high for all of these tumors. On the basis of these data it can even be concluded that patients with symptoms that are ascribed to a possible recurrence or 2nd primary tumor, more often have no recurrence than that they have one (Table 3, Chapter 2).

Improving the screening test used during follow-up

In the current follow-up program, routine visits consist of history taking and a complete head-and-neck examination including indirect laryngoscopy.

The accuracy of ultrasound-guided fine-needle aspiration cytology to determine lymph node involvement is about 89% compared to a 70% detection rate by palpation of the neck.[14] In our study group (n=402), 24 patients developed a regional recurrence during follow-up and in another 10 patients in combination with a local recurrence a positive lymph node was detected. If ultrasonography of the neck had been done during every routine visit, 4639 routine echograms would have been made in our study group. If we cautiously state that in the most optimal situation, the 34 patients with a regional recurrence would have been detected asymptomatically, then the detection rate due to routine ultrasonography would be less then 1%. It must be realized that there is no clear evidence that the date of death will be altered if standard ultrasonography of the neck were to be added to the follow-up examination.

The results of screening for primary lung malignancies by means of routine chest X-rays were disappointing. Critics will note that a chest X-ray probably lacks the sensitivity needed for early detection. A study by Swensen et al. (2005) in which heavy smokers were screened using a CT-scan showed that screening led to many false-positive results. No reduction in lung cancer mortality was achieved by earlier detection of the lung tumor.[15] On the basis of our own findings and supported by other studies, we have to conclude that routine chest X-rays for early detection of a primary lung tumor does not lead to an increased chance of survival in laryngeal cancer patients.[9,16] A more sensitive form of screening consisting of a spiral CT-scan in combination with a PET-scan would probably be of added value, but as yet there is insufficient evidence to support this. It should be noted that this form of screening would also lead to a very high rate of false-positive results.

Feasible screening program

In this thesis, only a slight reduction in the expected life expectancy of 50-70 year-old male laryngeal cancer patients is predicted if all routine follow-up visits were to be abolished. The implementation of a perfect follow-up program in which all recurrences are detected asymptomatically would improve life expectancy by 2.5

and 0.5 years for 50- and 70-year-old males, respectively.[12] However, increasing the asymptomatic recurrence detection by intensifying the follow-up schedule is not felt to be feasible due to the large number of routine visits (219-280) that would have to be conducted to detect 1 local or regional recurrence.[11]
At this moment, there are no standard prognostic tests available to distinguish aggressive tumors from indolent or slowly growing malignancies; this is an obstacle to any form of individually modified follow-up program.

The intention of the therapy given
The therapy given should be more effective in the asymptomatic stage of the disease than in the symptomatic stage. The therapy offered to patients with an asymptomatically detected local or regional cancer recurrence did not differ from that in the symptomatic patients with regard to either the intention of the therapy (curative or palliative) or the type of therapy (surgery or radiotherapy).[11]
The evaluation of all types of cancer recurrence, i.e. second primary head-and-neck tumors and primary lung malignancies, also revealed no difference in the type of therapy given or the intention of the therapy between asymptomatic and symptomatic patients.[8]

The number of patients in the "Detectable preclinical phase"
Since the estimated lead-time in the currently applied follow-up program is 2-4 weeks, an insufficient proportion of the screened population will be in the DPCP. As explained earlier, it will not be easy to increase the lead-time without increasing the work load enormously. It is quite clear that due to the short lead-time, it is not to be expected that there will be a large difference in survival between the asymptomatic and symptomatic group. It will also not be easy to increase the number of asymptomatically detected recurrences.

Psychosocial guidance
The routine follow-up examinations are often carried out by varying doctors during office consultations organized for that purpose. Guidance of the patient in connection with the sometimes permanent handicaps and the signaling of anxiety or a depressive disorder are usually not looked upon as the primary goal of routine follow-up. A prospective study reported by De Leeuw et al. (2000) revealed that the level of cognitive function before treatment and, to a lesser degree, being married were independent prognostic factors for the development of a recurrence and survival in patients with carcinoma of the head and neck.[17] Depressive moods and even vital depressions are regularly overlooked in patients with carcinoma of

the head and neck; it is advisable to pay attention to this even before the beginning of treatment. There are a number of risk factors that are important in this connection: female sex together with a high tumor stage and the presence of depressive symptoms before the start of treatment.[18] De Graeff et al. (2000) support these findings. Their study demonstrated that most of the post-treatment morbidity (surgery or radiotherapy) disappears again within 1 year and that there is a gradual improvement in psychological function and overall quality of life up to baseline level during the first 3 years of follow-up.[19] It turns out that an accurate prediction as to the risk of depression after 6 and 12 months of follow-up can be made by evaluating a number of factors, including the emotional support and the extent of the social network before the start of treatment (surgery or radiotherapy).[20]

Quality control over one's own actions, the treatment of complications and scientific research

Laryngeal cancer can lead to significant morbidity, especially when laryngectomy is carried out. Especially patients with recurrent cancer following extensive primary treatment run an increased risk for the development of both tumor-specific and therapeutically induced complications.[10] It is obvious that follow-up is necessary for the treatment of complications and in order to obtain insight into the effect of the therapy. Part of these medical follow-up examinations, and especially the evaluation of late complications, could well be performed by a simultaneously working oncology nurse.

The quality control over the primary therapy requires only a brief period of follow-up or specific check-ups designed for that purpose at intervals of, for example, one year.

Follow-up is not always required to determine the survival of two treatment groups.[3] When a new form of treatment is introduced, however, it is necessary to measure the disease-free survival accurately and to compare it with the current therapy. Such a prospective study will usually, however, be carried out in the form of a trial. A follow-up program with a scientific question that has not yet been established can be implemented if desired, but it is then advisable to work with standard forms so that sufficient information will be available retrospectively. The number of routine follow-up examinations that are required for scientific research is, however, significantly lower than the present number.

Costs

A cost-benefit analysis evaluates both the costs and the gain in health, both expressed in terms of money so that a profit-and-loss assessment can take place. This type of cost analysis is rare in healthcare. Other approaches are the cost-efficacy analysis and the cost-utility analysis, both of which are often used in healthcare. In a cost-efficacy analysis, the costs incurred are set out against a specific measure of health, often in the form of clinical indicators. In a cost-utility analysis, the costs are set out against the quality-adjusted life years.[21] When measuring the costs, both the direct costs within (such as the cost of an operation) and outside of the healthcare system (such as travel costs) and the indirect costs (employee absenteeism) can be included.[22]

It is questionable whether a reduction in the number of routine follow-up examinations would lead to savings in the direct medical costs. There can be no doubt that the number of additional check-ups at the request of the patient would increase, but the degree to which is difficult to predict. The economic savings that might be obtained by reducing the number of follow-up examinations could also lead to additional cost savings from a reduction in the number of supplemental tests. However, the costs to society might be increased by an increase in morbidity and mortality.

In view of the problems described above, cost savings are, for the time being, not looked upon as the decisive factor in the discussion regarding the follow-up program.

Future considerations

An extensive study by Brouha et al. (2003) showed that, despite a slight decrease in the overall incidence of larynx carcinoma, patients present with a T4-tumour relatively more often now than in the past; the difference was, however, not statistically significant. This phenomenon is clearer in the number of patients with a stage T4 carcinoma of the oral cavity (statistically significant) and less pronounced for patients with a stage T4 carcinoma of the hypopharynx. These findings are seen both nationally and internationally.[23] It is clear that the more frequent occurrence of relatively less favorable tumors must have an effect on the survival data. It should therefore be taken into consideration that this will lead to increase in the demand for care and will also affect the efficacy of the follow-up.

In the field of tumors of the oral cavity, “field cancerization” is a well-known concept.[24] Tabor et al. refined this concept. From a genetic point of view, a distinction should be made between a “second primary tumor” and a “second field tumor”; in the latter case, a genetically altered field leads to the development of a

new tumor.[25,26] Screening for local or regional recurrences and 2nd primary tumors in patients with such a genetically altered field may be useful, but this should be proven by future research.

Critical remarks

In the design of our study of the follow-up program, we have limited ourselves to an evaluation of the principal goal, the detection of asymptomatic recurrences. It is therefore impossible, on the basis of this study, to draw conclusions as to the efficacy with respect to a number of secondary goals. The secondary goals have, however, been mentioned and their relevance discussed. Until now, we are not aware of any studies in which the efficacy with respect to the secondary goals has been investigated.

For the study design, we chose the form of a longitudinal cohort study with a long intake phase. The data on the patients were obtained retrospectively, but the Departments of Radiotherapy and Otorhinolaryngology both maintained extensive and overlapping patient records, so that the data could be verified adequately. The design is in essence equivalent to that of a prospective study. A prospective study would be difficult to set up. It would, after all, be irresponsible to exclude patients from follow-up on a random basis so that the survival of patients with and without follow-up could be compared. Moreover, it is difficult to predict, beforehand, which factors should be randomized. For some risk factors (such as smoking), such prior randomization would be impossible.

Because future follow-up programs will also be investigated for their efficacy, we have attempted to develop a model with which the course of a malignant disease can be described. By applying this model, it will be possible to predict outcome measures such as life expectancy and cancer-specific mortality when new tests or other times for check-ups are added to the follow-up program. In our study we used a Markov model, suitably adjusted, that has been used previously to reach conclusions regarding screening for breast cancer. It should be emphasized that a model is only an imitation of reality. The results of the study must be interpreted in that light. As is also indicated in the discussion of the article in question, several types of models can be used and further research on this subject is recommended.[12]

Conclusions and recommendations

The above-mentioned studies have analyzed primarily the efficacy of asymptomatic recurrence detection. The following conclusions can be drawn from these studies:

- The hypothesis that asymptomatic detection leads to increased survival can be rejected.
- The presence of symptoms does not correlate with the severity of the disease.
- In the present follow-up program, the detection rate of asymptomatic recurrences is low, due to the very short lead-time.
- The specificity of symptoms is very low.
- Of all local and regional recurrences, 88% occur during the first 3 years of follow-up.
- Applying the same extensive follow-up schedule to patients who have already undergone very extensive treatment would appear to be of no benefit given the lack of therapeutic options if a recurrence is detected.
- Screening for second primary lung tumors leads to earlier diagnosis without any improvement in the therapeutic options or survival time.

If a follow-up program aimed at the early detection of a recurrence or second primary tumor were to be designed, the following three questions would be of great importance: Are the investigative methods used sufficiently sensitive? How often should routine visits take place and how long should the follow-up period be? At present, it can be concluded that for early detection of recurrences a follow-up duration of 3 years is sufficient for laryngeal cancer patients. The patients have usually achieved psychological stability and a global quality of life within 3 years.[19] Reducing the number of routine visits and the duration of follow-up will, in all likelihood, hardly lead to any reduction in life expectancy. Increasing the frequency of routine visits from once every 2 months to once a month would not be expected to lead to any major shift in the therapies used or to a longer survival time, given the short lead-time.

An oncology nurse and/or the original referring physician could carry out the routine visits alternately. It is very important to discuss the aim of the follow-up program with the patient. It is also important to explain the warning symptoms to the patient, while at the same time bearing in mind the risk of fixation on physical symptoms. Once it has been established that there are no more therapeutic options in the possible event of a recurrence, the follow-up program should be put aside and the focus should shift to care rather than cure.

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Summary

There is an ongoing public discussion regarding the purpose of routine follow-up programs following oncological therapy. The frequency and duration of a large number of these programs are determined historically on the basis of expert experience and the scientific data that would verify their efficacy is sometimes lacking.
The principal goal of the follow-up program as formulated for patients with laryngeal carcinoma is the pre-symptomatic detection of local and regional recurrences. This thesis examines the efficacy of the present follow-up program in achieving this goal.

The points requiring special attention during secondary screening are listed in the *Introduction* to this thesis. The assessment of the efficacy of a follow-up program after the treatment of cancer encounters the same difficulties as in the assessment of screening of the general population for primary carcinoma. The expected increase in the prevalence of larynx cancer in the Dutch population makes an evaluation of the present time-consuming follow-up program a timely exercise.

Chapter 2 describes a study cohort of 402 patients with squamous cell carcinoma of the larynx, treated in a way that was meant to be curative, who presented at the otorhinolaryngology outpatient clinic of the St Radboud UMC between 1990 and 1995. Of all the routinely planned follow-up examinations, 98% actually took place. In this cohort, 156 patients (39%) developed a local or regional recurrence, a 2nd primary tumor or distant metastases. Subdivided according to tumor localization, 94 patients developed a local or regional recurrence, 32 developed a primary lung tumor or a 2nd primary in the head-and-neck region, and 15 developed metastases. The maximum duration of follow-up was 10 years. More than 78% of all the above tumors developed during the first 3 years of follow-up. Most of the local and regional recurrences were detected during a routine follow-up examination when symptoms were already present. Analyses showed that there was no difference in the cancer-specific mortality or survival between patients with an asymptomatic and those with a symptomatic recurrence. The follow-up examinations hence did not achieve the stated goals: improvement of survival or reduction of the cancer-specific mortality.

Chapter 3 deals with the efficacy of the asymptomatic detection of primary lung tumors after the treatment of larynx cancer. Due to nicotine abuse, patients with a

laryngeal carcinoma are at increased risk for the development of a lung tumor. They are screened for this by means of routine chest X-rays. The follow-up program consisted of 7 routine chest X-rays during the first 5 years of follow-up: every 6 months during the first 2 years and then annually for the next 3.
This retrospective cohort study included 476 patients. The median duration of follow-up was 51.8 months. During this period, 2008 chest X-rays were made, including both planned X-rays and additional ones due to symptoms. Twenty-five patients developed a primary carcinoma of the lung. Only 16% of these were detected during the first 2 years of follow-up. No less than 32% were detected after the 5th year of follow-up. During the first 3 years after treatment, routine chest X-rays reveal mainly lung metastases.
There was no difference between the asymptomatic and symptomatic patients in survival. For both groups, the median survival was 56 months. An equal percentage of the patients in both groups could be operated. There was no difference in the tumor-specific mortality. On the basis of the results of this study, it was concluded that screening for primary carcinoma of the lung by means of chest X-rays is pointless.

In *Chapter 4***,** a subgroup of patients was evaluated that have a poor prognosis in case of tumor recurrence. This group included 259 patients that had undergone total extirpation of the larynx due to either an extensive primary tumor or a recurrence following prior irradiation. Eighty patients developed a recurrence following the laryngectomy. Of the recurrences, 50% developed within 9 months and 90% developed within 2 years of the follow-up program. Despite the frequent follow-up examinations during the first 2 years of the follow-up program, the recurrence was detected in only 16 patients (20%) while they were still free of symptoms. Treatment that was meant to be curative was offered to only 27.5% of the 80 patients with a recurrence. There was no difference between the asymptomatic and symptomatic patients in survival. The post-recurrence phase was characterized by considerable morbidity. Of all patients with a recurrence, 50% died within 6 months after detection. The results of this study imply that an oncological follow-up period of 2 years might suffice for this group of patients and that the follow-up should be based more on “care” than on “cure”.

Chapter 5 deals with the possibility of distinguishing a group at high risk for the development of a local or regional recurrence on the basis of clinical prognostic factors. For this purpose, we used data from the earlier study described in chapter 2. Patients with a combination of the factors cT-stage 2-4, continuing to smoke

after the diagnosis and a histologically poorly differentiated tumor have a risk of 29% for the development of a local or regional recurrence during 5 years of follow-up. The remaining patients constituted the low-risk group with a recurrence risk of 15%. Despite the intensive follow-up program, the percentage of all the recurrences that could be detected asymptomatically was low: 20%. Calculations showed that the lead-time, the length of time that the date of tumor detection was brought forward by the current follow-up program, was 2-4 weeks. It was therefore concluded that the current program does not suffice for the early detection of local and regional recurrences.

In *Chapter 6* we attempt to reach a conclusion regarding the expected reduction in survival time and increase in cancer-specific mortality if the routine follow-up examinations were to be abolished. For this purpose, a statistical Markov model was developed with 7 stages of health and 2 possible mortalities. Four hypothetical patient groups aged 40, 50, 60 and 70 years old, respectively, were introduced into the model. On the basis of data from the literature and our own empirical data, we calculated the effect of different follow-up protocols: the current protocol, a protocol in which all follow-up examinations are abolished, and the "perfect" follow-up protocol in which all tumors are detected in the asymptomatic phase. The results revealed a reduction in life expectancy of 0.8 and 0.3 years, respectively, for 50- and 70-year-old men if all routine follow-up examinations were to be abolished. The cancer-specific mortality increased by 4.9% and 2.8%, respectively, in the two age groups, but seems to be overestimated by this model. On the basis of this study, it can be concluded that the number of routine follow-up examinations could well be reduced with only a slight negative effect on the life expectancy and cancer-specific mortality. On the other hand, if it were possible to implement a perfect follow-up protocol, then the life expectancy of 50- and 70-year-old men would be increased by 2½ years and 6 months, respectively.

Chapter 7 contains the discussion on the basis of the results of this doctor's thesis. The main purpose of the routine follow-up examinations after the treatment of cancer is the detection of asymptomatic recurrences. However, the rate of asymptomatic detection turns out to be low, due especially to the short lead-time. There is hardly any gain in survival or reduction of cancer-specific mortality when the recurrence is detected in an asymptomatic stage. It is recommended that the follow-up program be adjusted to the personal needs of the patient. Part of the follow-up examinations can be carried out by an oncology nurse. Following the

treatment of laryngeal carcinoma, a follow-up duration of 3 years instead of 10 years would suffice.

Samenvatting

Er is een maatschappelijke discussie gaande over het doel en de behaalde resultaten van de routinematig uitgevoerde nacontrole schema's na een oncologische behandeling. Een groot aantal van deze schema's zijn qua frequentie en duur, historisch bepaald door ervaringsdeskundigen en missen soms wetenschappelijke data ter verificatie van de effectiviteit.
Het hoofddoel van het nacontrole schema zoals geformuleerd voor larynx-carcinoom patiënten is de pre-symptomatische detectie van lokaal en regionaal recidieven. In dit proefschrift wordt de effectiviteit van het huidige nacontrole schema t.a.v. het verwezenlijken van dit doel onderzocht.

In de *Inleiding* van dit proefschrift worden de aandachtspunten ten aanzien van secundaire screening op een rijtje gezet. In de evaluatie van de effectiviteit van een follow-up programma na de behandeling van kanker, treden dezelfde moeilijkheden op als tijdens de evaluatie van de algemene bevolkingsonder-zoeken. De verwachtte stijging van de prevalentie van larynxkanker in de Nederlandse bevolking maakt de evaluatie van het huidige tijdrovende nacontrole schema actueel.

Hoofdstuk 2 beschrijft een studiecohort bestaande uit 402 in opzet curatief behandelde patiënten met een plaveiselcelcarcinoom van de larynx die zich tussen 1990 en 1995 op de polikliniek keel-neus en oorheelkunde van het UMC St Radboud presenteerden. Van alle routinematig geplande nacontroles, gecorrigeerd voor overleving en tumor recidief, heeft 98% daadwerkelijk plaatsgevonden. In de cohort ontwikkelden 156 (39%) patiënten een lokaal of regionaal recidief, een (2^{de}) primaire tumor of metastasen op afstand. Uitgesplitst naar tumorlokalisatie ontwikkelden 94 patiënten een lokaal of regionaal recidief, 32 patiënten een primaire longtumor of een 2^{de} primaire tumor in het hoofd-hals gebied en 15 patiënten metastasen. De maximale follow-up bedroeg 10 jaar. Ruim 78% van alle voornoemde tumoren presenteerden zich in de eerste 3 jaar van de follow-up. De meeste lokale en regionale recidieven werden tijdens een routine nacontrole ontdekt terwijl er al symptomen aanwezig waren. Analyses toonden aan dat er geen verschil is tussen patiënten met een asymptomatisch of een symptomatisch recidief met betrekking tot kankerspecifieke sterfte en survival wat betreft locoregionale recidieven, 2^{de} primaire hoofd-hals tumoren, primaire longtumoren en metastasen. Het uitvoeren van nacontroles leidt derhalve niet tot

de gestelde doelen: verbetering van de overleving of reductie van de kankerspecifieke sterfte.

Hoofdstuk 3 behandelt de doelmatigheid van screenen op primaire longtumoren na behandeling van larynxkanker. Door nicotine-abusus lopen patiënten met een larynxcarcinoom een verhoogd risico op de ontwikkeling van een tumor in de longen. Door het routinematig verrichten van röntgenfoto's van de longen werd hierop gescreend. Follow-up bestond uit 7 routine röntgenfoto's van de longen in de eerste 5 jaar van de follow-up; om het half jaar in de eerste 2 jaar daarna jaarlijks tot 5 jaar follow-up.
In deze retrospectieve cohort studie werden 476 patiënten geïncludeerd. De mediane follow-up bedroeg 51.8 maanden. In deze periode werden er 2008 röntgenfoto's van de longen verricht (zowel geplande als additionele wegens symptomen). Vijfentwintig patiënten ontwikkelden een primair longcarcinoom. Slechts 16% hiervan werden ontdekt in de eerste 2 jaar van de follow-up. Maar liefst 32% na het vijfde follow-up jaar. In de eerste 3 jaar na behandeling worden met name longmetastasen ontdekt op de routine thoraxfoto's.
Er blijkt geen verschil te zijn tussen asymptomatische patiënten en symptomatische patiënten met betrekking tot de overleving. De mediane overleving bedroeg voor beide groepen 56 maanden. Een even groot percentage patiënten in beide groepen kon worden geopereerd. Er was geen verschil in tumorspecifieke sterfte. Op basis van deze studie is de conclusie getrokken dat screenen op primaire longcarcinomen door middel van röntgenfoto's ondoelmatig is.

In *hoofdstuk 4* wordt een subgroep met een slechte prognose in geval van recidief tumor, geëvalueerd. Een groep van 259 patiënten die een totale larynxextirpatie hadden ondergaan wegens een uitgebreide primaire tumor of tumorrecidief na eerdere bestraling, werd bestudeerd. Het effect van het optreden van recidiefkanker op mortaliteit en morbiditeit werd geanalyseerd. Tachtig patiënten ontwikkelden een recidief. Vijftig procent van de recidieven trad op binnen 9 maanden en 90% binnen 2 jaar van het follow-up programma. Ondanks de vele nacontroles in de eerste 2 jaar van het follow-up schema werd het recidief bij slechts 16 (20%) patiënten asymptomatisch ontdekt. Van de 80 patiënten met een recidief werd slechts aan 27,5 % een in opzet curatieve therapie aangeboden. Er werd geen verschil gevonden in overleving tussen asymptomatische en symptomatische patiënten. De postrecidief fase werd gekenmerkt door aanzienlijke morbiditeit. Vijftig procent van de patiënten met een tumorrecidief overleed binnen 6 maanden na detectie. De resultaten van deze studie impliceren

dat een oncologische follow-up van 2 jaar zou kunnen volstaan voor deze groep patiënten en meer gebaseerd moet zijn op “care” dan op “cure”.

Hoofdstuk 5 gaat in op de mogelijkheid tot het samenstellen van een hoogrisico groep op het ontwikkelen van locoregionale recidieven op basis van klinische prognostische factoren. Om dit te bepalen werden gegevens van de eerdere studie gebruikt zoals beschreven in hoofdstuk 2. Patiënten met een combinatie van de factoren; cT- stadium 2-4, doorgaan met roken na de diagnose en een histologisch slecht differentieerde tumor, hebben een 5-jaars risico van 29% op het ontwikkelen van een lokaal of regionaal recidief tijdens follow-up. De laagrisico groep had een risico van 15%. Ondanks het intensieve follow-up schema was het aantal asymptomatisch opgespoorde recidieven laag, ongeveer 20%. Berekeningen wijzen uit dat de lead-time, de tijd waarmee de detectiedatum van de tumor naar voren wordt gebracht met het huidige follow-up schema, 2-4 weken bedraagt. De conclusie is dan ook dat met betrekking tot het vroegtijdig opsporen van lokaal en regionale recidieven het huidige toegepaste schema niet voldoet.

In *hoofdstuk 6* wordt getracht een uitspraak te doen over de te verwachten reductie van de levensverwachting en toename van de kankerspecifieke sterfte indien de routinematige nacontroles zouden worden afgeschaft. Hiertoe werd een Markov-model ontwikkeld met 7 gezondheidsstadia en 2 sterftestadia. Vier hypothetische patiënten groepen werden in het model ingevoerd respectievelijk 40, 50, 60 en 70 jaar oud. Met behulp van literatuurgegevens en eigen empirisch data materiaal werd het effect berekend van verschillende follow-up protocollen: het huidige protocol, het protocol waarin alle nacontroles zijn afgeschaft en het “perfecte” follow-up protocol waarin alle tumoren asymptomatisch zouden worden opgespoord. De resultaten lieten een reductie van de levensverwachting zien van 0,8 en 0,3 jaar voor mannen van 50 resp. 70 jaar oud, bij afschaffen van alle routine nacontroles. De kankerspecifieke sterfte steeg met 4,9% en 2,8% respectievelijk in beide groepen, maar lijkt door dit model overschat. Op basis van deze studie kan gesteld worden dat reductie van het aantal routine nacontroles kan geschieden met zeer gering negatief effect op de levensverwachting en kankerspecifieke sterfte. Wanneer het daarentegen mogelijk zou zijn een perfect nacontrole schema uit te voeren, stijgt de levensverwachting van 2,5- 0,5 jaar voor mannen van 50 resp. 70 jaar oud.

Hoofdstuk 7 bevat de discussie op basis van de resultaten van deze promotie-studie. De routine nacontroles na behandeling van kanker zijn met name gericht op asymptomatische recidief detectie, echter de asymptomatische detectie blijkt mede door een korte lead-time laag te zijn. Er is geen overlevingswinst of reductie van kanker specifieke sterfte indien het recidief in een asymptomatische fase is ontdekt. Het is aan te bevelen het nacontrole schema aan te passen aan de persoonlijke behoeften van de patiënt. Een deel van de nacontrole momenten zouden verricht kunnen worden door een oncologisch verpleegkundige. Na behandeling van een larynxcarcinoom volstaat een follow-up duur van 3 jaar in plaats van 10 jaar.

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Curriculum Vitae

Savitri Christine Ritoe werd geboren op 11 maart 1972 te Paramaribo in Suriname. In 1990 behaalde zij haar middelbare school diploma aan het Stedelijk Gymnasium te Haarlem. In hetzelfde jaar startte zij met de studie geneeskunde aan de Rijksuniversiteit te Leiden. Na het doctoraal examen deed zij in de periode van 1995-1996 onderzoek aan afdeling obstetrie en gynaecologie van de Universiteit van Edinburgh, Schotland, naar de rol van Inhibine-A in chromosomaal normale en abnormale zwangerschappen. In 1998 werd het artsexamen aan de Rijks Universiteit van Leiden afgelegd. Daarna was zij werkzaam als basisarts op de afdeling heelkunde in het Diaconessenhuis Leiden van 1998 tot juli 1999 en vervolgens als basisarts op de afdeling keel- neus- en oorheelkunde aan het Antonie van Leeuwenhoek ziekenhuis te Amsterdam tot december 1999. Op 1 december 1999 werd zij aangenomen door de afdeling keel- neus- en oorheelkunde en hoofd / hals chirurgie aan het UMC St Radboud te Nijmegen. Er werd begonnen met het onderzoek naar het post-oncologische follow-up schema voor larynxcarcinoom patiënten. Op 01-07-2001 werd gestart met de opleiding tot keel-neus- en oorarts. In het laatste jaar van haar opleiding koos ze voor de differentiatierichting rhinologie en aangezichtschirurgie. Op 01-07-2006 werd de opleiding afgerond. Momenteel is zij werkzaam als KNO-arts aan het Academisch Medisch Centrum te Amsterdam.